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ASPERGILLOSIS AND THE ASPERGILLI

Report of a Unique Case of the Disease

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ANN ARBOR, MICH.

PLEBEIANS among fungi, members of the great group Aspergillus have attained chief notoriety as vexatious laboratory contaminants. Considerably less attention has been focused on their aptitude as instigators of disease, while their role as serviceable implements of medicine has received minimal consideration.

Aptly labeled "weeds" of the culture room,[1] over three hundred and fifty authenticated strains of aspergilli have been identified and delineated subsequent to their initial description in 1729. To warrant classification as an Aspergillus, a microscopic fungus must be comprised fundamentally of a stalk and a spore-bearing head. Innate minor variations occur in profusion, and though a species may be tentatively identified without undue difficulty, precise designation not infrequently entails recourse to a monograph devoted to this genus of molds exclusively.[1]

The aspergilli prosper in diverse circumstances, and their ability to thrive on foodstuffs, soil and a host of seemingly barren mediums is attested to by detailed laboratory precautions often maintained for their exclusion. Though species of this mold almost invariably throttle bacteria and other fungi attempting to proliferate on the same culture medium, the morphologic response of the former in such circumstances is at times so atypical as to render identification a laborious and protracted task. Little difficulty need be anticipated in culturing and grossly classifying material from clinical sources, however, since the colony may be readily recognized as a component of this genus on the basis of its resemblance to a field of ripening grain, in which stalks and heads predominate.[1] Examination of the aerial growth under a low power of the microscope reveals details of the spore-bearing or fruiting head and other features of taxonomic significance. A preponderance of species grow best at a temperature of 37 C., although

From the Department of Dermatology and Syphilology, Medical School, University of Michigan.

1. Thom, C., and Church, M. B.: The Aspergilli, Baltimore, Williams & Wilkins Company, 1926.

Aspergillus fumigatus has adequately demonstrated its ability to survive prolonged temperatures as low as —12 C., and certain of the aspergilli were, before the advent of modern refrigeration, commonly the derivation of distinctive molds on meat in storage room. Adequate oxygen tension is a prerequisite to the development of fruiting heads, though mycelium apparently proliferates under relatively anaerobic conditions. This doubtless accounts for the abundance of filamentous forms, often accompanied with chlamydospores and occasionally with bulbous terminal structures representing abortive heads, which may be discerned infiltrating the tissues in microscopic sections in cases of aspergillosis.

THE ASPERGILLI AS IMPLEMENTS OF MEDICINE

Flavicin, extracted from a strain of Aspergillus flavus and penicillin, both purified by the same method to an activity of 500 Oxford units per milligram, are reputedly similar in their chemical and antibiotic properties.[2] Another product of A. flavus, aspergillic acid, in contrast, to flavicin, has been shown to inhibit the growth of human strains of Mycobacterium tuberculosis, and suggestive evidence is presented to indicate that the mode of action of aspergillic acid can be explained on the basis of interference with the utilization of iron by the tubercle bacillus.[3]

Derivation of a partially purified preparation from A. fumigatus and the subsequent experimental study demonstrated the material to have bacteriostatic activity against M. tuberculosis BCG in a 1 : 1,400,000 dilution and bacteriocidal efficacy against the same organism in a dilution of approximately 1 : 700,000.[4] The authors reporting these results were not inclined to consider animal experiments concerned with toxicity and activity of the product until preparations of greater purity were available. It was postulated that the active substance may have been allied to helvolic acid, or purified fumigacin.

Other observers have determined that the mold Aspergillus fumigatus Fresenius affords several crystalline metabolic products, no less than three of which possess high antibacterial activity.[5]

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2. Bush, M. T.; Goth, A., and Dickinson, H. L.: Flavicin: An Antibacterial Substance Produced by an Aspergillus Flavus, J. Pharmacol. & Exper. Therap. **84**:262 (July) 1945.

3. Goth, A.: The Antitubercular Activity of Aspergillic Acid and Its Probable Mode of Action, J. Lab. & Clin. Med. **30**: 899 (Nov.) 1945.

4. Asheshov, I. N., and Strelitz, F.: An Antibiotic Substance Active Against Mycobacterium Tuberculosis, Science **101**:119 (Feb. 2) 1945.

5. Birkinshaw, J. H.; Bracken, A., and Raistrick, H.: Studies in the Biochemistry of Micro-Organisms: Metabolic Products of A. Fumigatus Fresenius, Biochem. J. **39**:70, 1945.

On the basis of these and a few other reports already available, enthusiastic prognostications as regards the future of antibiotics derived from the aspergilli appear to be well founded.

THE DISEASE ASPERGILLOSIS

Relatively few species of aspergilli have manifested pathogenicity for human beings. Perusal of available authentic data indicates that A. fumigatus has been isolated with greatest frequency from infections caused by the fungus, succeeded rather closely by Aspergillus niger. Aspergillus glaucus, A. flavus and Aspergillus nidulans are others implicated on occasion. Of worldwide consequence, the disease has been unearthed most often in warm, damp climates, and, as with other mycoses, more males than females are affected.[6] Aspergillosis has been disclosed in a child of 30 months and in an adult aged 77 years, though in most cases it apparently occurs in the decades of middle life. Asymptomatic infections caused by these fungi have been encountered on occasion.[7]

Pathologic alterations incited by the aspergilli are hardly unique. Microscopic scrutiny of the granulomatous lesions which eventuate reveals focal zones of necrosis containing the organism in varied stages of maturity and attended by a multifarious cellular infiltrate. Abscesses of diverse configuration and magnitude may supervene after coalescence of such lesions. Although metastatic dispersal of the fungi has not been verified in man, there is ample presumptive evidence to denote such an occurrence.

DIAGNOSIS

The reputation maintained by these fungi as frequent contaminants militates against a diagnosis of aspergillosis unless the evidence for such a conclusion is well founded and steadfast. Direct examination of suspected material may reveal filaments and spore-bearing heads. Presence of only the former, however, does not exclude this disease from the realm of diagnostic possibilities and may merely signify an oxygen supply which is inadequate for fruition. Repeated cultures of the organism in conjunction with stringent efforts to eliminate the likelihood of it being simply a contaminant are estimable and, in combination with the occurrence of fungi in biopsy specimens, of diagnostic import. The significance of immunologic reactions is equivocal. There is a paucity of precise information concerned with antibody response to

6. Conant, N. F., and others: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1945.

7. Donaldson, J. M., Jr.; Koerth, C. J., and McCorkle, R. G.: Pulmonary Aspergillosis, J. Lab. & Clin. Med. **27**:740 (March) 1942.

aspergillus infections,[6] although some authors have expressed the opinion that this fungus, in contrast to certain others designated, does not provoke the development of agglutinins.[8] A positive cutaneous reaction to an extract or vaccine does not discriminate between mere presence of the organism within the body and its role as an instigator of disease. Successful inoculation of animals lends credence to the belief that this fungus is causing a given infection, while failure does not exclude pathogenicity in other situations and in varied circumstances.[1] Roentgenograms, especially in pulmonary aspergillosis, may furnish presumptive evidence of mycotic etiology. In essence, a forthright and indisputable diagnosis of aspergillosis may be difficult of attainment. Microscopic specimens revealing the organism in tissues, combined with repeatedly positive cultures, are adequate for practical purposes.

CLINICAL MANIFESTATIONS

There is considerable speculation as to when aspergillosis may be labeled primary and when it is engrafted on tissues previously impaired by other disease processes. Inadequately controlled diabetes, carcinomatosis, tuberculosis, bronchiectasis, sepsis, cirrhosis of the liver, dysentery, enteritis [9] and even syphilis [8] have been cited as predisposing factors, and a proportion of patients with bronchial asthma and allergic rhinitis are reputedly sensitive to this mold. The term primary aspergillosis would appear to be best suited for cases in which the patients acquired the condition after prolonged exposure to massive doses of the organism and are without discernible evidence of other diseases. In a preponderance of recorded cases the disease has been of the secondary variety.

Once the organism has gained a foothold in the human host, a varied clinical picture may eventuate. Otomycosis has been publicized as the most frequently encountered manifestation of aspergillosis, although there is ample corroboration for the expressed opinion that the organism thrives in the cerumen of the external auditory canal most often as an ingenuous saprophyte,[10] accompanied on occasion with erythema, scaling and crusting merely as sequels to mechanical irritation.

Pulmonary aspergillosis is prone to occur, because of vocational hazard, in farmers, feed mill workers, fur cleaners utilizing rye flour for removal of grease, threshers and others having protracted and intimate

8. Wahl, E. F., and Erickson, M. J.: Primary Pulmonary Aspergillosis, J. M. A. Georgia **17**:341 (Aug.) 1928.

9. Van Ordstrand, H. S.: Pulmonary Aspergillosis with Report of a Case, Cleveland Clin. Quart. **7**:66 (Jan.) 1940.

10. Dodge, C. W.: Medical Mycology, St. Louis, C. V. Mosby Company, 1935.

contact with birds or grains, and pneumomycoses instigated by the aspergilli have recently been dignified by their legal accession to the category of occupational diseases.[11] Onset of the disease is usually insidious, although it may on occasion be brusque. The course of chronic pulmonary aspergillosis may, and not infrequently does, simulate that of pulmonary tuberculosis, while the acute variety is most often reminiscent of either bronchitis or pneumonia.[9] Varied roentgenologic patterns have been described, the early changes being at times indistinguishable from those of tuberculosis.[9] In an aggregation of 61 patients suspected of having pulmonary tuberculosis, painstaking scrutiny of sputum disclosed aspergillosis in 1,[8] and there appears to be general concurrence of opinion that the disease, masquerading under the guise of tuberculosis, may be more frequent than was previously suspected. The possibility of mycelial fragments retaining acid-fast stain, resulting in confusion with Koch's bacillus, is one to be borne in mind.[8]

Attention has been directed to the aspergilli as a cause of onychomycosis within recent years, a series of 13 cases having been cited in one communication.[12] Nails of both hands and feet may be involved, the clinical picture closely simulating that caused by other fungi. Greenish discoloration of the nail plate contingent on growth of the mold is at times helpful in gross differentiation. Simultaneous infection of nails with both a species of Aspergillus and Trichophyton rubrum has been reported.[12]

Protean manifestations of aspergillosis exclusive of those previously described may, on occasion, challenge the most astute clinician. Osseous involvement has been recorded, though infrequently. Subsequent to extrusion of a small foreign body from the swollen finger of a 13 year old Negro, there developed a fluctuant swelling on the back accompanied with roentgenographic evidence of destructive changes in several vertebrae and ribs. Culture of purulent materia aspirated from the lesion on the back resulted in a pure growth of A. fumigatus.[13] An abscess of the cerebrum instigated by a species of this genus has been encountered,[14] as has also a fatal aspergillosis of the meninges.[15] Dacro-

11. Coe, G. C.: Primary Bronchopulmonary Aspergillosis, an Occupational Disease, Ann. Int. Med. **23**:423 (Sept.) 1945.

12. Bereston, E. S., and Waring, W. S.: Aspergillus Infection of the Nails, Arch. Dermat. & Syph. **54**:552 (Nov.) 1946.

13. Shaw, F. W., and Warthen, H. J.: Aspergillosis of Bone, South. M. J. **29**:1070 (Nov.) 1936.

14. Just, E.: Aspergillus Abscess of the Cerebrum, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**:540, 1931.

15. Linck, K.: Fatal Aspergillus Meningitis in Man, Virchows Arch. f. path. Anat. **304**:408, 1931.

cystitis occurring in 1 patient and blepharitis in another were depicted as ophthalmic complications of aspergillus infections primary in the nose.[16] Deep black pigmentation of the vaginal wall distinguished such a mycotic infection involving this portion of the reproductive tract in an 8 year old girl, and the recorders unearthed only one comparable report in the literature.[17] Further illustrative of this fungus in the role of mimic was the case of a patient manifesting cervical and axillary adenopathy in combination with pulmonary pathologic symptoms who was regarded originally as being afflicted with tuberculosis, subsequently regarded as having Hodgkin's disease and ultimately proved to have aspergillosis of both lymph nodes and of the pulmonary structures.[8] Complete occlusion of the pulmonary artery by an elongated thrombus comprised essentially of this mold has been encountered at autopsy. The filiform structure pursued smaller arteries to their terminal branches, and the walls of the vessels were perforated at numerous sites by mycelium.[8] Aspergilli were isolated from a pericecal abscess on one occasion, and lesions of the spleen, kidneys and duodenum have been described, the majority occurring in conjunction with fatal pulmonary aspergillosis.[8] The diagnosis of primary cutaneous aspergillosis is difficult of establishment, and the condition is probably of relatively infrequent occurrence. Mycetomas have, however, been ascribed to this organism on occasion, and A. fumigatus has been demonstrated as a secondary invader in a gunshot wound of the chest.[8]

Discovery of aspergilli in the feces of patients with pellagra occasioned a furor in medical circles at one time. The strain isolated was productive of strong fluorescence when cultured, and it was postulated that absorption from the gastrointestinal tract of photodynamic substances evolved by these fungi might be a factor in the causation of pellagra.[18] Though alluring, this theory has not received widespread recognition. As concerns the danger associated with ingestion of mold-tainted foods, it is more than probable that these fungi are the conspicuous but usually harmless cause of damage or decay, in which situation, however, they are accompanied with bacteria or other organisms which are not grossly apparent yet which may be and often are dangerous.[1] The presence of mold in such situations is interpreted, therefore, as a warning.

Evidence has been adduced within recent years which indicates that many cases of reputed arsenical wallpaper poisoning, seldom an indis-

16. Rosenvold, L. K.: Dacrocystitis and Blepharitis Due to Infection by Aspergillus Niger, Am. J. Ophth. **25**:588 (May) 1942.

17. Weinstein, L., and Lewis, R. M.: A Case of Fungus Infection of the Vagina, Yale J. Biol. & Med. **11**:85 (Oct.) 1938.

18. Jobling, J. W., and Arnold, L.: The Etiology of Pellagra, J. A. M. A. **80**:365 (Feb. 10) 1923.

putable medical entity at best, were actually examples of infection with aspergillosis.[19] Chemical analyses performed in at least 2 cases labeled as instances of this type of poisoning did not reveal sufficient quantities of the chemical to warrant an etiologic relationship, and numerous investigators have noted an abundant growth of mold on wallpaper which supposedly was implicated as the source of the arsenic. Clinical manifestations on frequent occasions have been analogous to those encountered with pulmonary aspergillosis, and the green particles, supposedly arsenic, inhaled by the patients were probably in many instances the green spores of A. fumigatus.[19]

Notwithstanding the alleged efficacy of an imposing array of reputed therapeutic agents, treatment of aspergillosis is often unsatisfactory. The sulfonamide compounds and the newer antibiotics have not, so far as can be ascertained, proved especially valuable, and reliance must continue to be placed on intensive and prolonged administration of the iodides. An established diagnosis of this disease, especially as it concerns visceral cases of long standing, must entail in most instances a circumspect prognosis.

REPORT OF A CASE

B. O., a white infant, was born on July 15, 1938. No physical abnormalities were detected when the child was examined shortly after birth, but a roentgenogram of the chest at the age of two weeks demonstrated bronchopneumonia.

On Dec. 28, 1940, the child was admitted to the Pediatrics Service of the University of Michigan Hospital because of an apparently inflammatory consolidation of the medial portion of the lower lobe of the right lung, which had been manifest since resolution of the bronchopneumonia at the approximate age of six weeks. At no time had the patient been severely ill, and sulfonamide compounds by mouth had on numerous occasions effected an apparently evanescent amelioration in objective manifestations. There were no abnormal physical findings other than the area of consolidation, and the roentgenologist was of the opinion that tuberculosis, suppurative pneumonitis and pulmonary abscess could not be excluded from the realm of diagnostic possibilities. The results of laboratory studies were well within normal limits, and after two weeks of hospitalization, a course of sulfonamide drugs having been administered, the child was discharged, the film of his chest showing a moderate amount of clearing at the involved site.

By midyear of 1942 the patient had had oft repeated bouts of slight fever accompanying manifestations of a mild respiratory infection, the roentgenogram of his chest on each occasion exhibiting consolidation of the lower lobe of the right lung. One episode was associated with pleural effusion on the right side. Direct examination, culture and inoculation of the exudate into guinea pigs were not productive of etiologic clues. In August 1942 the child was readmitted to the hospital with a tender, fluctuant mass approximately the size and shape of a child's hand located at the lower costal margin in the left anterior axillary line. A roent-

19. Hay, H. R.: Arsenical Wallpaper Poisoning or Aspergillosis, J. Trop. Med. & Hyg. **42**:126 (May 1) 1939.

genogram of the chest revealed an unidentified but localized periosteal lesion involving the sternal portion of the left seventh rib and underlying the soft tissue tumor. Culture of purulent material aspirated from the lesion on two occasions resulted in the growth of a mold, subsequently identified as A. fumigatus.[20] Incision and drainage of the abscess demonstrated it to be of a multilocular structure.

At the age of 5, after two years of moderately good health, the child was found on roentgenologic examination to have pneumonia of the lower lobe of

Fig. 1.—Granulomatous foci involving the leptomeninges. These lesions contained an abundance of mycelial and filamentous structures but did not encroach on the cerebral cortex in this area. (Low power.)

the left lung, with minimal accumulation of pleural fluid at the left base. During subsequent months he had a persistent fever, the temperature ranging as high as 102 F. Administration of sulfonamide drugs appeared to be ineffective, and

20. Dr. C. W. Emmons, Principal Mycologist, United States Public Health Service, identified the organism.

a course of penicillin resulted in no notable improvement. Comprehensive laboratory studies, with exception of the cultures previously described, had been consistently noncontributory.

As a semi-invalid, the patient remained at home until January 1946, when, at the age of 7½ years, he began to have frequent episodes of dizziness, occipital headache, projectile vomiting and staggering gait. On admission to the hospital he had pneumonia of both lower lobes and demonstrable evidence of a cerebellar lesion, which was found at operation to be an abscess and from which A. fumigatus was again cultured. Despite intensive and protracted treatment which included administration of penicillin, various sulfonamide compounds, potassium iodide and inhalations of ethyl iodide, the child's condition became progressively worse

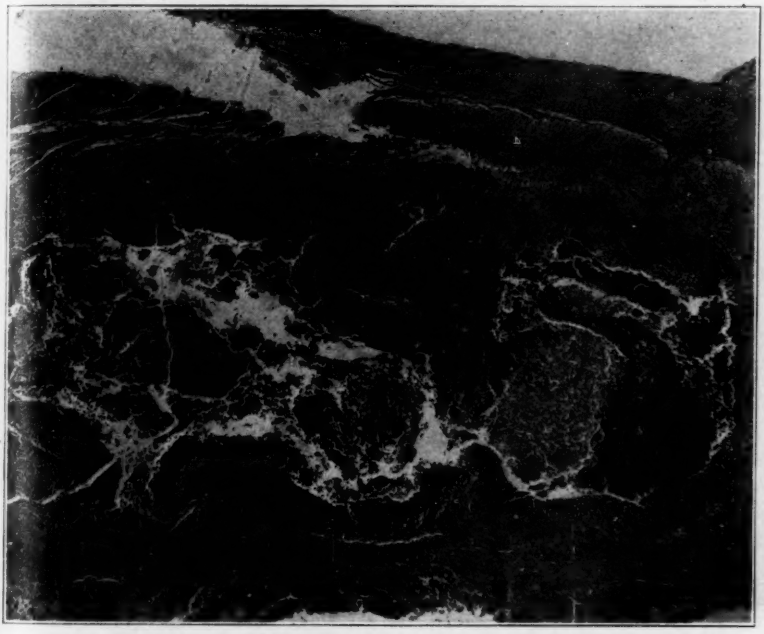

Fig. 2.—Mycotic myocardial abscesses involving the entire thickness of the wall of the left ventricle. (Low power.) The photomicrograph presented as figure 4 was made from the lesion at the left.

and recurrent abscesses, from several of which A. fumigatus was isolated, developed on the thoracic wall, the forehead and the right ankle. Death intervened on Sept. 6, 1946.

Complete necropsy was performed under the direction of Dr. C. V. Weller, Professor of Pathology, University of Michigan Medical School. Abscesses of variable size involving the brain, dura, heart, lungs, mediastinum, lymph nodes, spleen, liver, right kidney and right ankle were noted grossly. There was fibrinopurulent bronchitis, lobular pneumonia, obliterative fibrous pleuritis and an old perforation of the left thoracic wall, with associated abscess formation. Decubital

ulcers were present over the sacrum and the right posterior-superior iliac region of the spine. Early generalized atherosclerosis was apparent, as was also serous atrophy of all adipose tissue. Numerous cultures inoculated from various sites were productive of a growth of A. fumigatus.

Subsequent microscopic changes were especially notable. The dura mater showed an organizing subacute pachymeningitis, with frequent hemosiderin-laden phagocytes, an abundance of granulation tissue and surface necrosis. In the purulent exudate were numerous mycelial and filamentous structures, possessed of terminal and intercalary bulbous dilatations. Beneath areas in which the fungus was apparent in profusion there occurred a layer of multinucleate giant cells of the Langhans type, with, in addition, abundant lipid histiocytes.

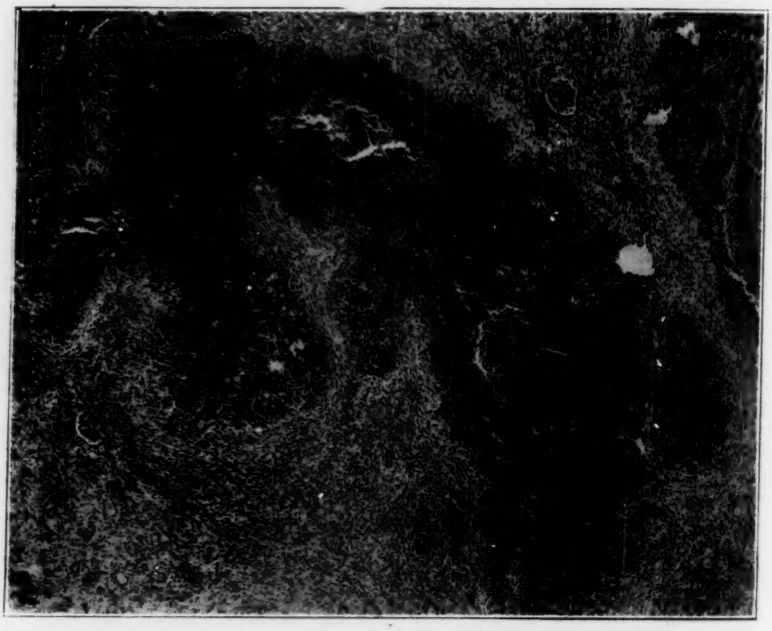

Fig. 3.—A moderately large granulomatous renal lesion. Numerous such foci were present in the kidneys, but myceliums occurred in sparse numbers. Partially destroyed glomeruli are apparent in the upper right and lower left hand corners with, in addition, a few tubules at the latter site. (Low power.)

The leptomeninges of the brain were markedly thickened, and there was an associated exudate similar to that noted in conjunction with the dura (fig. 1). An active base of granulation tissue partially limited abscessed areas containing the fungus from the brain itself, but there was patchy involvement of the cerebral cortex. Occasional foci exhibited a caseous type of necrosis. The cortex of the brain also revealed pronounced acute passive congestion and edema.

Microscopic sections of the heart showed granulomatous tissue involving the subepicardial adipose layer, the root of the aorta and the wall of the right atrium

in addition to relatively large myocardial and subendocardial abscesses which had ruptured into the left ventricle (fig. 2). Several of these same sites were infiltrated by variable numbers of organisms comparable to those previously described. Early coronary artery atherosclerosis was apparent.

The lungs revealed a widespread fungus-instigated pneumonitis accompanied with granulomatous masses similar to those previously described as occurring in the meninges. Mycotic abscesses were apparent in the spleen, liver, kidneys (fig. 3) and lymph nodes.

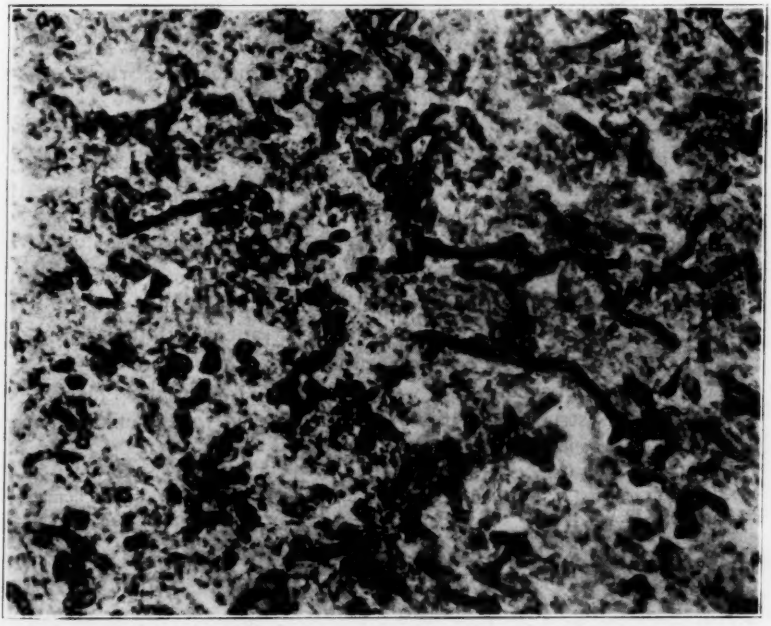

Fig. 4.—Numerous mycelial and filamentous structures, having terminal and intercalary bulbous dilatations, as they occurred in the abscesses involving the left ventricular wall. (High power.)

COMMENT

Though admittedly not verified, it would appear that this child's aspergillosis may have been implanted at the time of or shortly after birth. Indisputable, however, is the possibility that the disease was superimposed at a later date on pulmonary structures adequately prepared for such an invasion by a previously existent lesion.

Consistently normal results from laboratory studies, with the exception of cultures positive for A. fumigatus, were a feature of the disease process. Pneumonia, tuberculosis, suppurative pneumonitis and

pulmonary abscess were the roentgenologic diagnoses which appeared to be among the most logical explanations for a pulmonary lesion which in retrospect may well have been caused by A. fumigatus.

Aspergillosis involving virtually every major structure of the body to a variable extent has not previously been recorded, so far as can be ascertained, and suggests hematogenous dissemination of the organism. Invasion by the mold of such structures as the myocardium and kidneys was especially remarkable.

The frequent presence of atheromatous lesions throughout the arterial tree of the bronchopulmonary system is a feature common to all types of pulmonary aspergillosis [21] and emphasizes the probable cause of a grossly demonstrable atherosclerosis in the case reported.

SUMMARY

The aspergilli, a genus of molds, are notorious as laboratory contaminants. On rare occasion they may be the etiologic agent in production of a specific disease, and in other circumstances they may, as a source of antibiotics, function as serviceable implements of medicine.

Manifestations of the disease aspergillosis are protean, and the diagnosis may be difficult of establishment. The lungs are most frequently the site of primary involvement. Treatment is often disconcerting, there being no specific therapeutic agent.

A unique case of aspergillosis with extensive and widespread involvement of various structures is reported, accompanied with details of the gross and microscopic pathologic changes.

21. Jacobson, H. P.: Fungous Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1932.

ERYTHEMA NODOSUM

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AND
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ERYTHEMA nodosum, a disease characterized by transient nodules on the skin resembling bruises, may also be accompanied with fever and migratory arthritis. The common, mild form is usually seen and treated by dermatologists, while the severer examples are observed in hospitals, in which attention has been drawn to the systemic symptoms. It is the latter which have caused confusion over the many different conditions which may initiate erythema nodosum. Reviews of the voluminous literature on the subject [1] show how strongly entrenched the belief is that erythema nodosum is a form of either tuberculosis or rheumatic fever. Only recently has a plurality of causes been recognized and the role of hypersensitivity studied. A brief review of the obvious causes of erythema nodosum indicates how little clearcut information is available. For this reason the present clinical study has been arranged to describe the natural history of the disease. Such an approach should aid in the care of a random patient with erythema nodosum as well as improve the understanding of its complexities.

REVIEW OF THE LITERATURE

Tuberculosis.—The early observers [2] considered tuberculosis to be the cause of erythema nodosum. This view is still prevalent in the

From the Medical Clinic and Department of Radiology, Peter Bent Brigham Hospital, and the Department of Medicine and Radiology, Harvard Medical School.

1. (*a*) Wallgren, A.: Erythema Nodosum and Pulmonary Tuberculosis, Lancet **1**:359, 1938. (*b*) Ernberg, H.: Erythema Nodosum and Tuberculosis, Am. J. Dis. Child. **46**:1297 (Dec.) 1933. (*c*) Collis, W. R. F.: Erythema Nodosum, Lancet **2**:732, 1934. (*d*) Spink, W. W.: Pathogenesis of Erythema Nodosum, with Special Reference to Tuberculosis, Streptococcic Infection, and Rheumatic Fever, Arch. Int. Med. **59**:65 (Jan.) 1937.

2. (*a*) Chauffard, A., and Troisier, J.: Erythème noueux expérimentale par injection intradermique de tuberculine, Bull. med., Paris **27**:7, 1909. (*b*) Pollak, R.: Erythema Nodosum und Tuberkulose, Wien. klin. Wchnschr. **25**:1223, 1912. (*c*) Gutman, R. A.: Un cas de erythema noueux avec presence de bacilles de Koch dans le sang circulant, Paris méd. **21**:416, 1917. (*d*) Ernberg, H.: Das erythema nodosum, seine Natur und seine Bedeutung, Jahrb. f. Kinderh. **95**:1, 1921.

British [3] and Scandinavian [4] literature. It is founded on a limited number of objective observations. Occasionally new erythema nodes have been seen after a tuberculin test,[2a] which nodes are indistinguishable on biopsy from spontaneous lesions.[2d] Erythema nodosum has been observed at the time the reaction to the tuberculin test became positive in previously negative reactors.[5] It has been seen occasionally complicating miliary tuberculosis.[6] It has also been seen with hilar shadows in the roentgenogram of the chest,[7] although, as we shall show, this last evidence alone is equivocal.

Streptococcic Infections.—Another sparsely documented cause of erythema nodosum is infection with beta hemolytic streptococci. In this country sporadic cases have been reported.[8] The culture of beta hemolytic streptococci in material from the throats of patients with pharyngitis accompanying erythema nodosum [9] and the induction of remote lesions in patients with erythema nodosum with intradermal injections of streptococcic broth filtrates [1d] or streptococcic nucleoprotein [8c] suggest that streptococci are nevertheless a common cause of the disease.

Rheumatic Fever.—The tendency to classify erythema nodosum with the so-called hypersensitivity diseases (rheumatic fever, rheumatic states, polyarteritis nodosa, disseminated lupus erythematosus, glomerulonephritis and allergic purpuras) has clouded the relation of erythema

3. Symes, J. O.: Significance of Erythema Nodosum, Brit. J. Dermat. **44**:181, 1932. Footnote 1 *c*.

4. (*a*) Löfgren, S.: Primary Pulmonary Tuberculosis with Erythema Nodosum in Connection with B. C. G. Vaccination, Acta tuberc. Scandinav. **19**:231, 1945. (*b*) Wallgren, A.: Paratuberkulose Krankheitserscheinungen, in Engel, S., and von Pirquet, C.: Handbuch der Kindertuberkulose, Leipzig, Georg Thieme, 1930, vol. 1, p. 809; Tubercle Bacilli in Children with Erythema Nodosum: Demonstration by Gastric Lavage, Am. J. Dis. Child. **41**:816 (April) 1931. (*c*) Rotnes, P. L.: Untersuchungen über Erythema nodosum im erwachsenen Alter, Acta dermat.-venereol. (supp. 3) **17**:1, 1936. (*d*) Ernberg.[1b]

5. (*a*) Gamstedt, E.: Ueber die Tuberkulinempfindlichkeit bei Erythema nodosum vor der Eruption, Monatschr. f. Kinderh. **59**:111, 1933. (*b*) Meara, F. S., and Goodridge, M.: The Relationship Between Erythema Nodosum and Tuberculosis, with Report of a Case, Am. J. M. Sc. **143**:393, 1912. (*c*) Ernberg.[1b]

6. Landouzy, L.: Erytheme noueux et septicemies a bacillus de Koch, Bull. Acad. de méd., Paris **70**:400, 1913. Weber, R. P.: Erythema Nodosum with Tuberculous Bacillaemia and Meningitis, Brit. J. Child. Dis. **21**:119, 1924. Gutman.[2e] Meara and Goodridge.[5b]

7. Ernberg, H.: Erythema Nodosum, Nord. med. tidskr. **4**:230, 1932; footnote 2 *d*.

8. (*a*) Stone, W. R.: Erythema Nodosum Associated with Streptococcic Faucitis, New York M. J. **118**:673, 1923. (*b*) Goldstein, H. I.: Erythema Multiforme and Erythema Nodosum with Streptococcic Sore Throat, M. J. & Rec. **134**:266, 1931. (*c*) Pilot, I.: Focal Infection and Erythema Nodosum. J. A. M. A. **101**:2145 (Dec. 30) 1933.

9. Stone.[8a] Pilot.[8c]

nodosum and rheumatic fever to streptococcic infections. For instance, it has been noted that 11 per cent of patients with erythema nodosum have preexisting rheumatic heart disease,[1d] that migratory polyarthritis may be present in both conditions and that occasionally a prolonged P-R interval in the electrocardiogram or the new development of rheumatic murmurs has accompanied erythema nodosum.[10] Undoubtedly rheumatic fever does occur with erythema nodosum, but, as we shall show, it is unusual.

Other Diseases.—Erythema nodosum is a type reaction of specific tissues to selective agents. Its frequency in any one disease has been best studied in coccidioidomycosis (5 per cent of 8,000 cases[11]) and is similar to that observed in other infections (tuberculosis, 2 in 66 patients,[12] and streptococcic infections, 2 in 272 patients[13]) in which it is a rare manifestation of the common disease. Occasionally, syphilis,[14] lymphopathia venereum,[15] meningococcemia,[16] influenza,[17] measles,[18] dental infections[19] and chronic ulcerative colitis[20] have been accompanied with erythema nodosum.

Drugs.—Of interest because of the light shed on the pathogenesis of the disease is the ability of certain drugs to induce erythema nodosum.

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10. (*a*) Mackenzie, S.: On Erythema Nodosum, Especially Dealing with Its Connection with Rheumatism, Tr. Clin. Soc. London **19**:215, 1886. (*b*) Holmes, A. H.: Erythema Nodosum, Lancet **2**:784, 1934. (*c*) Claman, I. A.: Erythema Nodosum: A Link in a Rheumatic Syndrome, Am. J. Dis. Child. **48**:1448 (Dec.) 1934. (*d*) Markson, A.: Antistreptococcal Serum for "Rheumatic" Affections, Brit. M. J. **1**:129, 1935.

11. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health **30**:600, 1940.

12. Myers, J. A.; Diehl, H. S.; Boynton, R. E., and Trach, B.: Development of Tuberculosis in Adult Life, Arch. Int. Med. **59**:1 (Jan.) 1937.

13. Pilot, I., and Davis, D. J.: Sporadic Sore Throat, J. A. M. A. **97**:1691 (Dec. 5) 1931.

14. Fischl, F.: Erythema nodosum lueticum: Spirochätenbefund und Histologie, Arch. f. Dermat. u. Syph. **129**:361, 1921.

15. Hellerström, S.: A Contribution to the Knowledge of Lymphogranuloma Inguinale, Acta dermat.-venereol., 1929, supp. 1, p. 5. Amtman, L., and Pilot, I.: Lymphogranuloma Inguinale, Arch. f. Dermat. u. Syph. **26**:868, 1932. Pilot.[8c]

16. Master, A. M.: Meningococcemia with Endocarditis, J. A. M. A. **96**:164 (Jan. 17) 1931.

17. Boganovitch, V.: Five Cases of Post-Influenzal Erythema Nodosum, Arch. Dis. Childhood **5**:56, 1930.

18. Ernberg, H., and Gabinius, O.: Close Succession of Cases of Erythema Nodosum of Nontuberculous Pathogenesis, Am. J. Dis. Child. **57**:1012 (May) 1939. Spink.[1d]

19. Elwell, L. B.: Erythema Nodosum and Focal Infection, Brit. M. J. **1**:974, 1935.

20. Brooke, P. A.: Erythema Nodosum-Like Lesions in Chronic Ulcerative Colitis, New England J. Med. **209**:233, 1933.

Drugs act in two different ways. In the case of the sulfonamide compounds,[21] they may be a provocative agent for the disease being treated. This is a similar phenomenon to that seen in primary tuberculosis, in which erythema nodosum may follow inoculation with Bacillus Calmette-Guérin.[4a] The second mode of action is a primary effect of the drug itself, as, for example, erythema nodosum following iodine therapy.[22]

Sarcoid.—Although the cutaneous and pulmonary lesions of erythema nodosum have been claimed to be a form of sarcoid,[23] histologic evidence obtained during an attack of erythema nodosum has not been presented, nor does the clinical course of sarcoid[24] conform with that described here and elsewhere[25] for erythema nodosum.

CLINICAL MATERIAL

The patients with erythema nodosum in this study were observed in the Peter Bent Brigham Hospital and the Children's Hospital during the past thirty years. The majority of the group and those on whom the laboratory data have been more complete have come under observation during the past ten years. Among 102 adults, 88 were women (86 per cent), and among 53 children 12 years of age or younger, 32 were girls (60 per cent). The predominance of the disease in women after the age of puberty has been noted previously[26] and is found also in erythema nodosum due to coccidioidomycosis.[11] The age at the onset of disease varied from 3 to 66 years in the present study. The majority of the patients were between 20 and 40 years of age, and 20 were over 50 years old. The following are the summaries of 2 cases studied.

Case 1.—A 40 year old nursemaid entered the hospital on May 25, 1940, because of migratory polyarthritis and red lumps on her shins. The family history was noncontributory. At 9, 21 and 27 years of age she had isolated attacks of migratory polyarthritis. For five months she had tended a family of sickly children and had had one respiratory infection after another. Three weeks before her admission to the hospital a mild cough, sore throat and earache had developed.

Examination.—The temperature was 100.8 F., the pulse rate 90, the respiratory rate 24 and the blood pressure 108 systolic and 72 diastolic. There were typical

21. Löfgren, S.: Erythema Nodosum Following Treatment with Sulfanilamide Compounds, Acta med. Scandinav. **122**:175, 1945.

22. Perrin, L.: Un cas d'erytheme noueux du a l'iodure de potassium, Marseille-med. **29**:567, 1892.

23. Kerley, P.: (*a*) The Significance of the Radiological Manifestations of Erythema Nodosum, Brit. J. Radiol. **15**:155, 1942; (*b*) The Etiology of Erythema Nodosum, ibid. **16**:199, 1943.

24. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): A Study of Thirty-Five Cases, Am. Rev. Tuberc. **49**:289 and 437, 1944.

25. Grosse, A. H.: Erythema Nodosum: Analysis of a Hundred Cases, Practitioner **91**:240, 1913. Spink.[1d] Rotnes.[4c]

nodes on the shins, a clear throat, palpable cervical lymph nodes and a grade 2 systolic murmur over the precordium.

Laboratory Data.—The urine was normal. The red blood cell count was 3,830,000, the hemoglobin content 11.5 Gm., the white blood cell count 11,400 and the total protein content 7.0 Gm. per hundred cubic centimeters, with 4.1 Gm. of albumin and 2.9 Gm. of globulin. Reactions to tests with first and second strength purified protein derivative were negative. Roentgenograms made during the illness and one year later are shown in figure 1. An electrocardiogram showed left axis deviation.

A follow-up examination one year later showed a normal condition. No murmurs were present.

CASE 2.—A 37 year old housewife was admitted to the hospital on June 18, 1943, because of fever, migratory arthritis and red nodes on her shins of four weeks' duration and substernal distress for three days. As a child she had been exposed to tuberculosis in the household. A roentgenogram of her chest six years before was clear. There was no history of rheumatic fever in the family. The patient was

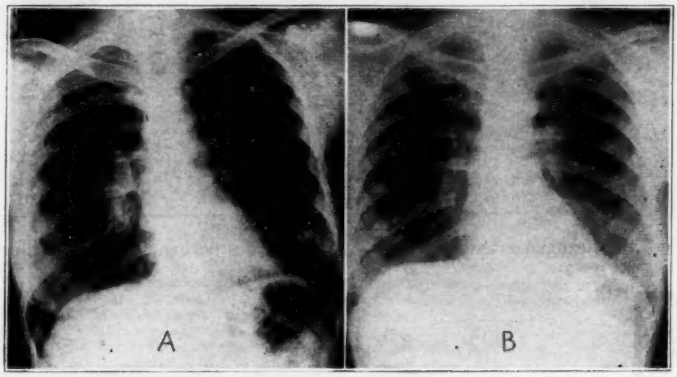

Fig. 1.—Roentgenograms in case 1. *A*, typical hilar nodes during the patient's illness. *B*, one year later.

obese, had mild angina pectoris, suffered with chronic sinusitis with postnasal discharge and had had recurrent sore throats, for which her tonsils had been removed twice.

Examination.—The temperature was 102 F., the pulse rate 120 and the respiratory rate 24. The weight was 190 pounds (86 Kg.). There were typical erythema nodes over the shins and atypical lesions on the arms. The mucous membranes of the nose and throat were injected, but no cervical adenopathy was present. The chest was clear to percussion and auscultation despite a chronic dry cough and the remarkable findings in the roentgenogram. The heart was normal.

Laboratory Data.—There was a negative reaction of the blood to the Hinton test, and the urine was clear. The red blood cell count was 4,300,000, with a hemoglobin content of 14.5 Gm. The hematocrit reading was 41. The sedimentation rate was 46 mm. in one hour (Wintrobe). The white blood cell count was 8,400, with 90 per cent polymorphonuclear cells. The total protein content was 6.4 Gm. per hundred cubic centimeters, and the fasting blood sugar content was 117 mg. The circulation time (decholin) was four seconds. The tourniquet test elicited a negative

reaction. The electrocardiogram contained normal curves. The roentgenogram of the chest showed the heart to be normal in size and the hilar nodes large, the node on the left being 7 cm. in diameter. In addition, there was coarse streaking in both pulmonary fields.

Course.—With rest in bed and symptomatic therapy, recovery was prompt. The cough subsided slowly. Follow-up examination of the heart and lungs and roentgenograms three years later revealed only persistent angina pectoris.

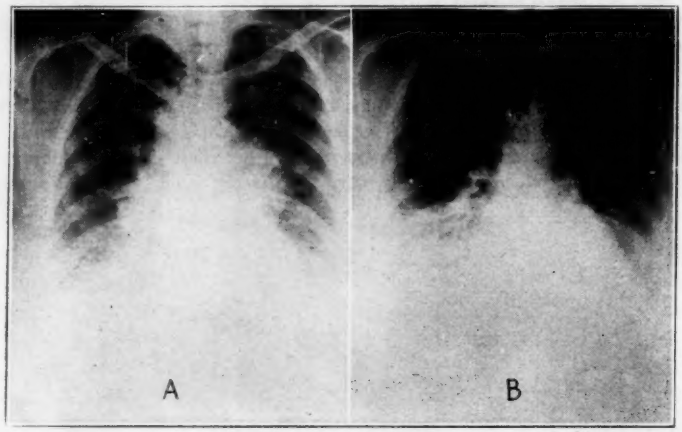

Fig. 2.—Roentgenograms in case 2. *A*, hilar nodes during the patient's illness. *B*, after recovery.

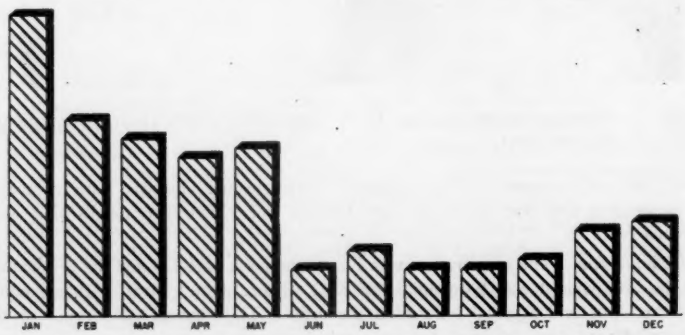

Fig. 3.—Seasonal incidence of erythema nodosum in 154 patients.

Season.—As has been noted previously,[25] January in particular and the winter months in general were the times when the greatest number of attacks occurred (fig. 3). In New England the peak in streptococcic infections is usually in February. In the San Joaquin Valley, where erythema nodosum is oftenest due to coccidioidomycosis, the greater number of attacks occur in the summer months.[11]

Family History.—The striking lack of rheumatic fever and tuberculosis in the detailed family histories in the hospital records is noteworthy. In the present group of 155 patients there were 15 who had a history of chorea or rheumatic heart disease in a parent, sibling, aunt or uncle. These will be discussed. Two of the 15 persons and 1 other patient in whose family there was no history of rheumatic disease also had a parent or sibling who had erythema nodosum.

Of the 155 patients, 3 gave a history of exposure to active tuberculosis and an additional 10 of exposure to tuberculosis in the household.

TABLE 1.—*Antecedent Infections in Patients with Erythema Nodosum*

	No. of Patients
Involvement of the Upper Respiratory Tract	
Pharyngitis	55
Tonsillitis	14
Peritonsillar abscess	3
Otitis media	2
"Infection of the upper respiratory tract"	16
Tonsillitis, tuberculous	1
Pharyngitis	1
Involvement of the Lower Respiratory Tract	
Sore throat, bronchitis, chest rales, low to normal white blood cell count	11
"Grip," sore throat, conjunctivitis and scleritis	3
Tracheobronchitis	8
Active apical tuberculosis, with tuberculous cervical lymph nodes	1
Miliary tuberculosis, terminal tuberculous meningitis at autopsy	1
Miscellaneous	
Conjunctivitis, previous parotitis	1
Conjunctivitis, cervical adenopathy, mild pharyngitis, low white blood cell count	2
Infected scalp, posterior cervical adenopathy, erythema nodosum	1
48 hours following injection therapy with "cold vaccine" for bronchitis	1
24 hours following passage of renal calculus	1
Persistent subcutaneous nodules	1
Erythema nodosum developing into classic ulcerative colitis	1
Acute gonococcic pelvic inflammatory disease	1
Cellulitis of the arm, axillary abscess, erythema nodosum	1
Abscessed teeth, erythema nodosum	3
Measles, sore throat, erythema nodosum	1
Scarlet fever, erythema nodosum	1

Past History.—A history of recurrent sore throats (table 1) was common. Although the respiratory infection which immediately preceded erythema nodosum often was so mild as to receive little attention from the patient or his physician, a long history of recurrent pharyngitis or chronic low grade sinusitis was more obvious. Comment is made on this point because it is in contrast to the relation between erythema nodosum and tuberculosis or coccidioidomycosis, in which erythema nodosum often accompanies the initial development of sensitivity to the infectious agent.

A past history of tuberculosis in the 155 patients was unusual. One person had a tuberculous hip as a child, while other patients who gave no known history of tuberculosis had various quiescent lesions (see roentgenograms).

Attacks of migratory polyarthritis lasting days to weeks, not accompanied with erythema nodosum, occurred one to twenty years before the onset of erythema nodosum in 20 of 103 adults (19 per cent) and in none of the children. Similar attacks have been observed after the onset of erythema nodosum in other patients (see account of follow-ups). The same phenomenon occurred in several of Spink's patients [1d] and was observed by Holmes.[10b] Of the 20 persons who had arthritis more than a year before the onset of erythema nodosum, 4 had a sore throat in association with the attack. Four others had an attack of arthritis which lasted several months. Still others of the 20 persons had two or three attacks of arthritis over a period of years, without subsequent damage to the joints or heart, and in 1 instance arthritis was accompanied with the typical perihilar lymphadenopathy of erythema nodosum but not with the cutaneous lesions. The strong similarity between the

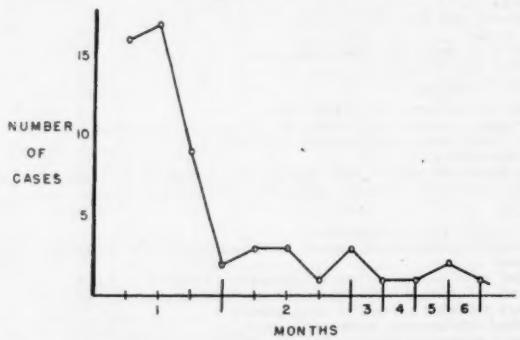

Fig. 4.—The lag between onset of infection and onset of erythema nodosum in 59 patients.

arthritis of erythema nodosum and so-called palindromic rheumatism [26] suggests that the latter may be a close relative to erythema nodosum.

Onset.—A known respiratory infection antedated erythema nodosum in 126, or 81 per cent, of 155 patients (table 1). The lag between the infection and the onset of erythema nodosum was usually two to four weeks (fig. 4).

In 4 of the 155 patients there was clinical evidence of active tuberculosis coincident with erythema nodosum. Two of these were children who had been exposed to the disease in the family, 1 of whom died of miliary tuberculosis six weeks after the attack of erythema nodosum.

26. Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism: A "New," Oft Recurring Disease of Joints (Arthritis, Periarthritis, Para-Arthritis) Apparently Producing No Articular Residue; Report of Thirty-Four Cases; Its Relation to "Angioneural Arthrosis," "Allergic Rheumatism" and Rheumatoid Arthritis, Arch. Int. Med. **73**:293 (April) 1944.

The second child had the signs of erythema nodosum only, but tubercle bacilli were recovered from the material obtained by gastric aspiration on inoculation of a guinea pig. In the third patient, a child without history of exposure to tuberculosis, typical erythema nodosum (without pains in the joints) developed after acute tonsillitis. Tonsillectomy some weeks later unexpectedly revealed tuberculous tonsils on biopsy (table 1). In the fourth patient, a young woman also without a history of exposure, there developed erythema nodosum associated with acute cervical adenitis. Biopsy of a cervical lymph node revealed caseous tubercles, and roentgenograms of the chest demonstrated an apical infiltration, probably inactive (see section on roentgenologic findings).

Physical Examination.—The one constant physical finding was the cutaneous lesion. It began as a firm, tender, subcutaneous nodule 1 to 2 cm. in diameter. Subsequently, edema and erythema, soon followed by a bruised appearance, developed in the overlying skin. Occasionally (5 patients) there was frank nonthrombocytopenic purpura manifested by ecchymoses into the nodules and at other sites in the skin. One patient had, in addition, recurrent bleeding from the mucous membranes of the pharynx and rectum. This phenomenon is similar to that in the condition in Traut's case [27] which he reported as erythema nodosum with Henoch's purpura. Lesions stopped at different stages of development and regressed in the time it took them to develop. Sometimes they coalesced and seemed to fluctuate but did not suppurate. The typical lesion on the shins occasionally measured 4 to 6 cm. in diameter and lasted a week or longer. As edema subsided, a fine cigaret-paper scale often formed. In one instance of chronic ulcerative colitis, recurrent ulcerations of the nodes on the shins took place over a period of months.

Although the characteristic location of the nodules was on the vulnerable tibial and ulnar surfaces, lesions also were seen on the soles of the feet and on the calves, thighs, buttocks, upper part of the arms, scalp and face. In individual patients the site of the lesions could be directly related to local trauma. Within an hour following steady pressure of a blunt object the beginning subcutaneous nodule could be felt. A bed cradle over the legs during the night and instructions to avoid crossing the legs greatly diminished the number and severity of lesions. Extensive exposure to sunlight was not deleterious to the patient.

Arthritis.—The second most characteristic physical finding was the arthritis with the disease. Eighty of 103 adults and 13 of 53 children had pains in the joints. The ankles, knees, wrists, fingers, elbows, shoulders, hips and back, in order, were the sites involved. Pain, local

27. Traut, E. F.: Hypersensitivity in Rheumatic Disease, M. Clin. North America **18**:1237, 1935.

swelling and occasionally redness and fluid were present. Often the bedridden patient had less involvement of the joints than the ambulatory patient. Arthritis before the appearance of nodes was as frequent as that appearing afterward (fig. 5).

Respiratory Infections.—The third commonest physical finding was evidence of a respiratory infection. Seventy of 155 patients had palpable cervical adenopathy—part of a recent or present infection of the throat. Nine patients had infections of the lower respiratory tract.

Heart.—Six of 155 patients were known to have rheumatic heart disease a year or more before the development of erythema nodosum. In none of these did cardiac lesions change during the present illness. Transient grade 1 or grade 2 apical systolic murmurs were heard in 50. In 6 of these the first mitral sound was also temporarily accentuated. Three other patients, children, left the hospital with suggestive systolic

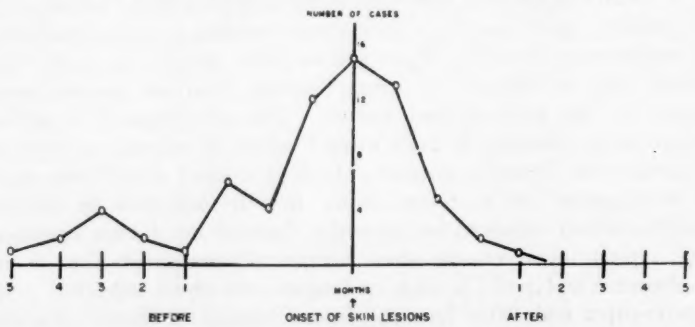

Fig. 5.—Interval between the time of arthritis and the appearance of the cutaneous lesions in 79 cases of erythema nodosum.

murmurs. Two of these had histories of rheumatic heart disease in the family and accordingly are classified as having potential rheumatic heart disease. In 1 of the 155 patients active carditis developed during the course of erythema nodosum. This was a child in whom a loud systolic and diastolic murmur developed over the precordium and who died within six weeks of acute rheumatic pancarditis (table 1). In a word, in only 1 of 155 patients did unequivocal evidence of rheumatic fever develop at the time of erythema nodosum.

Two patients had conjunctivitis and the periorbital cutaneous lesions which have been described with erythema nodosum.[28] Other physical abnormalities were occasionally present (table 1), but they were not a part of the clinical syndrome. It is of interest that the spleen was not palpable during the course of erythema nodosum in these patients.

28. Bluefarb, S. M., and Morris, G. E.: Erythema Nodosum of Face: Report of Case, Arch. Dermat. & Syph. **43**:802 (May) 1941.

LABORATORY OBSERVATIONS

Hemoglobin Content.—Mild secondary anemia was common. The hemoglobin content was above 13 Gm. per hundred cubic centimeters in one third of the patients, and below 10 Gm. in 15 per cent. Occasionally pronounced anemia was present.

White Blood Cell Count.—On admission of the patients to the hospital the white blood cell counts were most often normal. When pharyngitis and an elevation of temperature were present the counts usually ranged between 12,000 and 25,000, with some abnormality in the differential count. In patients with local cervical adenopathy presumably secondary to low grade pharyngitis, the white blood cell count also was frequently elevated, ranging between 11,000 and 24,000. On the other hand, the patients with infections of the lower respiratory tract, colds and grip had normal or low counts (8,800 to 1,800), with a normal differential count or with relative neutropenia.

Total Protein Content.—The total protein content was normal in 10 of the 12 patients for whom it was determined. In 4 the albumin-globulin ratios were within normal limits. In 2 others, who were tested many times, the globulin content was elevated during the acute phase of the disease, reaching 4.5 and 5.2 Gm. per hundred cubic centimeters respectively. Each of these last 2 patients had long severe illnesses, one shown to be of streptococcic origin and the other to belong to the group of infections of the lower respiratory tract.

Examination of Urine.—Transient slight albuminuria at the height of the disease was often present. Other urinary changes were not found.

Electrocardiograms.—Forty-nine out of 63 patients tested had normal tracings at various stages of their illness. Eleven patients, including 1 with hypertension and the child with acute carditis, had left axis deviation. One other patient with previously recognized rheumatic heart disease had right axis deviation. The 9 remaining persons with left axis deviation had normal hearts clinically.

Bacteriology.—Most of the bacteriologic studies were done on patients seen during the past five years. Cultures were made of material from the throat of 55 patients. No beta hemolytic streptococci were recovered from 28 persons for whom material was cultured once or from 2 for whom it was cultured twice. They were cultured one or more times in material from the remaining 25 patients. In material from several persons with recurring attacks of erythema nodosum they were cultured during attacks and could not be cultured in the intervals.

Material Used in Testing the Skin: Beta hemolytic streptococci recovered from the throats of patients with erythema nodosum or acute pharyngitis due to this organism were grown in tryptic digest broth for eighteen to forty-eight hours, washed three times by

centrifugation and resuspended in 0.85 per cent isotonic solution of sodium chloride, in a concentration of 1,000,000,000 organisms per cubic centimeter. The suspensions were killed by subjection to a temperature of 56 C. for thirty minutes on two successive days, with storage in the interval at 4 C., and sterility was checked by subculture in thyoglycolate mediums (Brewer). Patients were tested with 0.1 cc. of vaccine intradermally in the forearm. If a severe reaction could be anticipated from the presence of an obvious streptococcic infection, 1 : 10 or 1 : 100 dilutions were first tried.

Results: Reaction patterns were of two types, local and systemic. The local reaction consisted in induration, with an area of edema and erythema of a centimeter or more in diameter beginning often within twelve hours and usually becoming maximal in twenty-four hours. The systemic reaction usually began within five to twelve hours and consisted in increased malaise, arthralgias of the knees and ankles, at times with swelling of the joints, anorexia and sometimes a rise in the body temperature. For purposes of this study, well defined systemic reactions and/or the development of new erythema nodes following the cutaneous test were considered significant when the tests done at a different time with purified protein derivative, brucellergen, lygranum or an alpha streptococcus vaccine did not cause similar reactions.

Twenty-eight patients were studied with multiple tests of the skin. Fifteen of 17 in whom beta hemolytic streptococci were demonstrated in their throats by culture had a significant systemic reaction and an increase in nodes following the cutaneous test with beta streptococcus and not following other cutaneous tests. Eleven of the 13 other patients similarly tested gave a positive local streptococcic reaction only. Retesting 4 of the 15 patients who had had systemic reactions at a later time when their disease was mild or subsiding did not reproduce systemic reactions or nodes but did cause the local cutaneous reaction.

One patient gave a local and systemic reaction, including the appearance of new nodes, with an alpha streptococcus reaction and not with a beta hemolytic streptococcus reaction. Following extraction of two infected teeth, a febrile, incapacitating bout of erythema nodosum which had been smoldering for five months was abruptly terminated. The patient has remained well during a year of follow-up observations.

Tuberculin Tests.—Sixty-one patients were tested with purified protein derivative intradermally. Twenty-one of these were also tested with beta hemolytic streptococcus vaccine and showed a local or systemic reaction mentioned previously. Seven of the group tested with streptococcus vaccine and 22 others, or a total of 29 of the 61 patients, had positive cutaneous reactions to the first or second strength purified protein derivative. One of the 61, the patient who subsequently

died of miliary tuberculosis, was the only one who gave a systemic reaction to tuberculin.

Pathologic Process.—A biopsy of a cutaneous node was done on 5 patients. The findings were in keeping with previously reported changes.

Roentgenologic Study.—For 65 patients roentgenograms of the chest were made during the active stage of the disease (table 2). For 37, or approximately half of the group, the findings were entirely normal in all respects. Twenty-eight had pulmonary changes, but these were nonspecific and not characteristic in two thirds of them (18 patients). They usually revealed a slight accentuation of the normal pulmonary markings, similar to that seen in any acute respiratory infection or in acute bronchitis. Two of this group had fine, diffuse mottling of both lungs similar to that seen in the earliest stages of silicosis. Three others had small areas of localized apical infiltration. In 2 these were interpreted as areas of pulmonary tuberculosis, obsolete

TABLE 2.—*Roentgenologic Examination of the Chest in Sixty-Five Patients*

Entirely negative		37
Increased fuzzy markings		13
Enlarged lymph nodes		10
Bronchial only	6	
Bronchial and mediastinal	4	
Mottling of lungs		2
Apical infiltration		3
Total		65

in 1, and in the other (the patient with scrofula) of questionable activity. With respect to the third patient, material obtained by gastric aspiration was sterile on inoculation of a guinea pig and reactions to cutaneous tests with first and second strength purified protein derivative were negative during the acute illness and six weeks and twelve months later. The 10 patients who had enlarged lymph nodes either at the roots of the lungs (the true bronchial nodes) or in the upper mediastinum or in both sites were the only ones who presented characteristic symptoms. In 6 of these 10 patients the enlargement was limited to the bronchial nodes and was bilateral and fairly symmetric. In 3 there was a definite clear zone between the sharply outlined, lobulated shadows of the bronchial nodes and the mediastinal shadow of the heart and great vessels. This is the only pathognomonic sign by which the enlarged nodes of erythema nodosum can be differentiated from those of other forms of lymphadenopathy. It is not always present and not always clear, but when it is present and distinct it is highly suggestive (figs. 1 and 2).

Roentgenograms of the painful swollen joints were made for several patients, and some were repeated at later examinations. None of them

showed any abnormality of the joints and the adjacent bones were entirely normal except for occasional atrophy from disuse.

Roentgenograms of the nasal accessory sinuses showed a high percentage of chronic sinusitis. In some patients this condition may have been a significant part of their disease, as could be discovered by the proper bacteriologic studies. Since sinusitis alone is common in New England, the roentgenologic findings are not significant.

Well defined Ghon tubercles were rare in the entire group, and only 1 patient had calcification in the hilar glands already present at the time of erythema nodosum. One patient had a diagnosis of bronchiectasis confirmed by bronchograms, made with the use of iodized oil U. S. P., some time before the onset of erythema nodosum.

PROGNOSIS AND TREATMENT

Severity of Illness.—In most patients the temperature was 99 to 101 F. (37.2 to 38.3 C.) during the acute phase of the illness. Higher temperatures were observed as follows: 102 to 103 F. (38.9 to 39.4 C.) in 30 patients, 103 to 104 F. (39.4 to 40.0 C.) in 15 patients, 104 to 105 F. (40.0 to 40.6 C.) in 3 patients and 105 F. (40.6 C.) in 1 patient. Headache, nausea, malaise and asthenia were most prominent in the patients with high fever. The course was often phasic, in one to three day cycles, corresponding to the appearance of new lesions or further manifestations in the joints. Accompanying respiratory infections were slow to clear up. Usually a steady improvement followed symptomatic treatment. Occasional patients remained acutely ill for months despite supportive therapy. Two patients were abruptly improved by tonsillectomy for obviously infected tonsils. A similar improvement has been previously observed.[29] It should be emphasized, therefore, that if erythema nodosum has not subsided in the usual two to five weeks and if the tonsils are the likely source of the inciting infection, they should be removed without delay. Prophylactic doses of penicillin can be used to limit provocative temporary exacerbations which may follow. Equally important is the removal of other obvious sources of infection. Unless these are eradicated, erythema nodosum may smolder on for an indefinite period.

Chemotherapy.—One patient seemed to improve immediately after treatment with sulfadiazine. Many other patients did not respond to sulfonamide chemotherapy, and several patients treated with intensive courses of penicillin—240,000 units a day—by uninterrupted intramuscular injections each two hours did not recover more rapidly than would be expected without specific therapy. Roentgen treatment of

29. Spink.[1d] Pilot.[8c]

the pharynx to shrink hypertrophied lymphoid tissue lengthened the asymptomatic intervals in chronic relapsing erythema nodosum. Local irrigations of the throat, artificial fever therapy (typhoid, four chills) by the method of Solomon [30] and administration of salicylates were nonspecific modes of therapy used, without altering the course of the disease. Two patients, ill for more than five months with persistent febrile erythema nodosum, were brought to a state in which they were free from signs and symptoms and maintained there for a year following a course of desensitization with beta hemolytic streptococcus vaccine given subcutaneously in increasing nonreacting amounts, similar to the methods used for desensitization in hay fever. Each of these patients, however, has had a later recurrence of erythema nodosum during subsequent pharyngitis caused by beta hemolytic streptococci.

Duration.—Erythema nodosum is usually a self-limited disease of one to five weeks' duration. Attacks may smolder on in a subacute stage for three to nine months and occasionally for years (5 patients). In these unfortunate persons the symptoms are periodic in intensity and rarely completely absent. Ten per cent of the 155 patients had the chronic form of the disease. In other studies [1d] recurrence of erythema nodosum as well as a smoldering course has also been noted. In this series attacks recurred one to twenty years later (4 patients) or recurred several times at wide intervals in the same patient (6 patients).

Follow-up Examination.—A follow-up examination one year or longer after the onset of erythema nodosum was made on 61 of the 155 patients. Eleven patients gave a subsequent history of chronically recurring manifestations of erythema nodosum in the skin and joints over a period of two to ten years. Two of these persons had rheumatic heart disease, which had been recognized before the first evidence of erythema nodosum. Seven of the 61 persons, 2 of whom had rheumatic heart disease, had one or more isolated attacks of erythema nodosum following their first attack. Nine of the 61 patients had one or more bouts of arthritis without erythema nodosum at a later date. Two of these, each followed for a year, have retained a grade 2 systolic murmur, which is suggestive of early mitral disease, and in 1 patient who had a normal heart at the time of erythema nodosum rheumatic aortic insufficiency developed six years later. This last patient is the only one of the 61 in whom definite valvular disease developed after the attack of erythema nodosum. In other words, 5 of 61 patients followed up had rheumatic heart disease, but 4 of these had rheumatic heart disease

30. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccine, New York State J. Med. **41**:45, 1941.

before the development of erythema nodosum. In 1 patient mentioned elsewhere fatal rheumatic carditis developed during erythema nodosum.

Follow-up roentgenologic examinations of the heart and lungs were made a year or more after the acute stage of the disease in 30 patients. None of these patients showed any roentgenographic evidence of pulmonary tuberculosis, and in none of them had calcification developed in the bronchial nodes. The follow-up period ranged from one to twenty-six years and averaged five years.

The enlargement of the lymph nodes persisted from three to twelve months, usually disappearing in five to seven months. The pulmonary changes were more evanescent, usually disappearing in a few weeks, but persisting in 1 patient for several months. In none of this group were coarse nodular or streaking areas subsequently found in the lungs, such as would be expected in sarcoidosis and as were reported by Kerley.[23]

COMMENT

The multiplicity of unrelated infections and drugs known to initiate erythema nodosum has tended to obscure its common association with infections caused by beta hemolytic streptococci. In this series, not only was there a high incidence of respiratory infections antedating cutaneous lesions but also beta hemolytic streptococci were cultured in material from half of the patients who were studied bacteriologically. The occurrence of the disease with the physical evidence of other types of respiratory infections and during the season when these are prevalent suggests that a variety of common infectious agents are also the cause of erythema nodosum.

The low incidence of clinical tuberculosis is in contrast to the frequency of streptococcic infections associated with erythema nodosum. A limited number of tuberculin tests (29 out of 61 patients reacting positively) reflects only the incidence of positive reactors in the population at large in this region. In Rotnes' series a higher incidence was observed (94 per cent), but this may have another explanation. The pulmonary lesions which may accompany erythema nodosum have rarely been found to be due to tuberculosis in our series. Even individual patients with parenchymatous as well as hilar shadows in the roentgenograms of the chest have been found to be nontuberculous when carefully studied and followed up.

Our percentage of positive findings in roentgenograms of the chest is less than that in most series of cases, probably because we are including the milder forms of erythema nodosum. Kerley [23] has reported what we regard as a selected series of cases (28 out of 37 patients with positive signs in the roentgenograms), and, from his description, has included several patients with sarcoidosis. Paul and

Pohle[31] have emphasized the tuberculous nature of the disease in their group of 20 patients on whom roentgenograms of the chest were made, 9 of whom had some degree of glandular enlargement. Rotnes[4c] reported 110 of 181 patients (61 per cent) with pulmonary changes shown on roentgenologic examination. He classified the lesions as hilar adenitis (20 patients), hilar adenitis with parenchymatous changes (54 patients), parenchymatous changes only (22 patients) and other hilar changes (14 patients). Evidence from many sources suggests that erythema nodosum accompanying tuberculosis appears at the time the cutaneous reaction to tuberculin becomes positive, that is, during the primary complex. Although erythema nodosum may be produced with excessive amounts of tuberculin in previously sensitized persons, this pattern rarely occurs spontaneously. In these circumstances the pulmonary lesions accompanying erythema nodosum should follow the course of the primary complex. Unfortunately, Rotnes, Kerley, Paul and Pohle have not presented bacteriologic evidence of tuberculosis in their patients or evidence of follow-up examinations demonstrating subsequent fibrosis or calcification in the pulmonary fields. A limited number of follow-up examinations made on our patients has revealed a striking lack of subsequent evidence of tuberculosis.

If the pulmonary lesions of erythema nodosum are often not tuberculous, then how do they come about? In table 1 there are listed various forms of regional lymphadenopathy present during erythema nodosum. The commonest is cervical, presumably draining an infection of the throat. When the infection is at another site, as for instance on the scalp or arm, it is again the local lymph nodes which enlarge. It seems likely, therefore, that hilar adenitis is a similar regional adenopathy draining a pulmonary or bronchial infection or a profuse postnasal discharge.

We agree with Kerley[28] that roentgen treatment does not cause regression of the enlarged lymph nodes or hasten the course of the disease. In 1 of our patients a mild dose of roentgen rays to the mediastinum caused an unexpectedly severe general reaction. We would not advise roentgen treatment even as a diagnostic test. The same reaction has been noted after roentgen treatment of pulmonary and mediastinal sarcoidosis.

A final point is the relation of erythema nodosum to rheumatic fever. The evidence presented here suggests that erythema nodosum is not a form of rheumatic fever but occasionally may accompany or follow it. The history of similar disease in the family, common in

31. Paul, L. W., and Pohle, E. A.: Mediastinal and Pulmonary Changes in Erythema Nodosum, Radiology **37**:131, 1941.

cases of rheumatic fever,[32] was unusual for our patients. The frequency (11 per cent) of preexisting rheumatic heart disease at the time of erythema nodosum, which has been noted before [1d] and also in this study (4 per cent), is a reflection of the relation of the two diseases to streptococcic infections. Jones has pointed out that 65 per cent of young patients who have had rheumatic fever will show evidence of cardiac damage during a rheumatic attack and 86 per cent will have murmurs within eight years.[33] Although adults in whom rheumatic fever develops show a decreasing incidence of cardiac disease,[34] no such evidence as is reported by these observers followed erythema nodosum in this series. A follow-up for a longer term may reveal subsequent rheumatic heart disease, but studies on potential rheumatic heart disease at five and ten years [35] suggest that this is highly unlikely. It may be interesting to include erythema nodosum with rheumatic fever in the group of hypersensitivity diseases, but this is a generic rather than a direct relationship. The proper antigen in the properly sensitized and predisposed persons may produce erythema nodosum in 1 and rheumatic heart disease in another. The concurrence of the two diseases, however, is coincidental. For prognostic reasons, especially as regards life insurance, this distinction is important to make.

SUMMARY

1. The clinical features of erythema nodosum in 155 patients, 61 of whom were followed for one to twenty years, are presented.

2. The disease occurred oftener in women (86 per cent), appeared in patients at the ages of 3 to 66 years and usually developed during the winter months.

3. Associated respiratory infections accompanied 80 per cent of the attacks. In one half of the patients for whom cultures were done beta hemolytic streptococci were grown in material from the throat. Tuberculosis was an uncommon antecedent infection and rheumatic heart disease a rare sequela.

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32. Wilson, M. G., and Schweitzer, M. D.: Familial Epidemiology of Rheumatic Fever: Genetic and Epidemiological Studies, J. Pediat. **22**:468 and 581, 1943. Wilson, M. G.: Hereditary Susceptibility in Rheumatic Fever: The Potential Rheumatic Family, J. A. M. A. **124**:1188 (April 22) 1944.

33. Jones, T. D., and Bland, E. F.: Clinical Significance of Chorea as a Manifestation of Rheumatic Fever: A Study in Prognosis, J. A. M. A. **105**:571 (Aug. 24) 1935.

34. Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease: A Statistical Study, J. A. M. A. **121**:113 (Jan. 9) 1943.

35. Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Rheumatic Heart Disease" and Rheumatic Mitral Insufficiency, Am. J. M. Sc. **195**:764, 1938.

4. Migratory polyarthritis was a part of the clinical picture of erythema nodosum in 80 per cent of adults and in a third of the children. Isolated attacks of pains in the joints preceded and followed erythema nodosum. Ten per cent of the patients had a chronic form of the disease lasting from months to years.

5. Mild secondary anemia, cervical adenopathy and occasionally (13 per cent) enlarged hilar or bronchial nodes characterized the illness.

6. Erythema nodosum is thought to be a hypersensitivity disease. Individual predisposition, a variety of infectious and chemical agents and local trauma contribute to its occurrence. It is not a form of rheumatic fever.

BLOOD PRESSURE READINGS OF 75,258 UNIVERSITY STUDENTS

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MANY studies of blood pressure have been made on large numbers of persons of different ages representing supposedly normal, healthy people. From such studies certain ranges of blood pressure have been accepted as "normal" for various age groups, these "normal" ranges being in fact the averages of the groups. The examination of large samples of the population can add to the knowledge of what may be considered "normal," or at least most common, for the particular group examined. It is not our purpose to attempt to define the "normal" blood pressure for any age group, but to present data on blood pressure determinations on a large number of persons, most of whom are young adults.

In reviewing the literature, there is found rather wide variation in the average blood pressure levels in supposedly normal persons. Alvarez [1] found the systolic pressure in male university students to average 128.9 mm. of mercury, while the mean for the women was 117.3 mm. Diehl [2] reported blood pressure readings of male students at the University of Minnesota in the years 1922, 1923 and 1924. He found the mean systolic pressure to be 126.9 mm. in the year 1922. In 1923 and 1924 the mean systolic pressure was 122.7 mm. This difference was thought to be due to the fact that students having a systolic pressure of 140 mm. or more in the 1923 and 1924 groups were rechecked later in the examination; thus the effect of excitement on the blood pressure level was reduced, since the second reading was the one recorded. Robinson and Brucer [3] studied a group of supposedly healthy persons reporting for periodic examinations. In males between 15 and 45 years

From the Students' Health Service, University of Minnesota.

1. Alvarez, W. C.: Blood Pressures in Fifteen Thousand University Freshmen, Arch. Int. Med. **32**:17 (July) 1923.

2. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, Arch. Int. Med. **36**:151 (Aug.) 1925.

3. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure, Arch. Int. Med. **64**:409 (Sept.) 1939.

of age the mean systolic pressures were between 117.5 and 120.1 mm. In females in the same age groups the mean systolic pressures were between 107.4 and 119 mm.

TABLE 1.—*Systolic Blood Pressure of Men by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16	114	122.58	118.5	±1.1214	90 to 149
17	1,694	121.87	121.1	±0.3211	80 to 149
18	8,344	121.99	121.7	±0.1418	60 to 209
19	6,470	122.68	122.3	±0.1616	60 to 229
20	5,088	123.06	122.8	±0.1769	70 to 199
21	4,615	122.90	122.5	±0.1863	70 to 199
22	4,106	123.11	122.4	±0.1847	70 to 209
23	3,554	123.42	122.3	±0.1952	60 to 209
24	2,792	123.08	121.9	±0.2161	80 to 189
25	1,934	122.54	121.6	±0.2596	80 to 179
26	1,291	122.46	121.2	±0.3072	80 to 179
27	916	123.50	121.7	±0.3758	80 to 179
28	638	122.78	120.9	±0.4362	90 to 189
29	463	122.25	120.5	±0.5451	80 to 179
30	364	122.10	120.3	±0.5960	90 to 169
31 to 35	853	122.10	120.7	±0.4019	80 to 169
36 to 40	284	116.97	120.1	±0.8028	90 to 209
41 and over	281	119.79	122.8	±0.8603	80 to 189
Total	43,800	122.74	122.0	±0.0592	60 to 229

TABLE 2.—*Systolic Blood Pressure of Women by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16	159	107.35	109.2	±1.0094	70 to 149
17	2,182	108.14	108.8	±0.2600	70 to 159
18	7,432	106.94	108.3	±0.1442	60 to 179
19	4,753	108.66	109.2	±0.1789	60 to 179
20	4,273	110.85	111.0	±0.1833	60 to 219
21	3,604	112.97	112.4	±0.1844	70 to 179
22	2,786	113.28	112.9	±0.2064	70 to 169
23	1,555	112.34	112.7	±0.2807	70 to 189
24	956	112.98	113.0	±0.3699	80 to 169
25	633	112.67	113.0	±0.4403	70 to 159
26	427	112.95	112.3	±0.5561	60 to 159
27	306	113.82	113.6	±0.6288	80 to 149
28	299	113.00	113.9	±0.6887	80 to 159
29	237	113.54	113.6	±0.8866	90 to 149
30	226	114.57	115.1	±0.8027	90 to 159
31 to 35	820	114.12	115.5	±0.4586	70 to 189
36 to 40	442	115.90	116.7	±0.6007	90 to 179
41 and over	368	122.67	125.3	±0.9917	90 to 239
Total	31,458	110.61	111.0	±0.0693	60 to 239

The material for the present study was obtained from the records of physical examinations made at the Students' Health Service at the University of Minnesota from 1930 through 1942. During this twelve year period, 75,258 persons were examined, of whom 43,800 were men and 31,458 were women. With the exception of a few faculty members, the group comprised university students. The blood pressure readings were

made with a mercury manometer by the auscultatory method, with the student in a sitting position. In general, the diastolic reading was taken at the point at which the tone changed, although we cannot be certain that all examiners throughout the twelve year period conformed to this method.

The mean age for the men was 21.51 years, with a range from 16 to 70 years. The majority were between 17 and 26 years of age. For the women the mean age was 21.06 years, with a range from 16 to 66 years, and the majority were between 17 and 23.

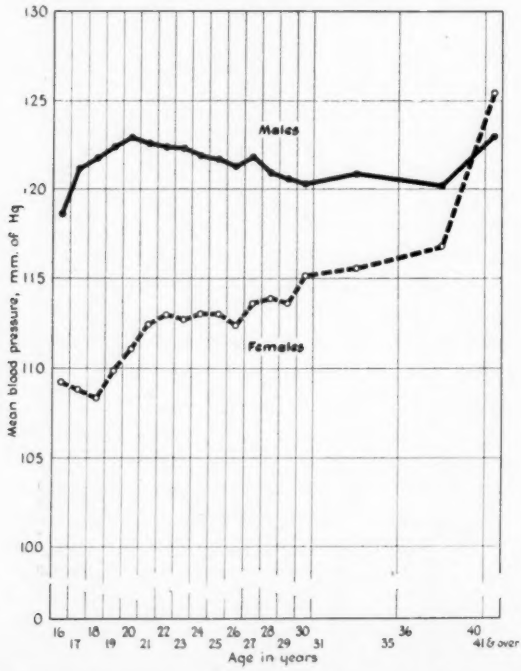

Fig. 1.—Mean systolic blood pressure by age and by sex.

The means and ranges of systolic blood pressure for each age group of men are presented in table 1. The same data for women are given in table 2. The mean systolic blood pressure for men of all ages included in this study was 122 mm., and for women, 111 mm. In every age group except the group over the age of 40 the mean systolic pressure in men exceeded that in women. The sex differences in mean systolic blood pressure are statistically significant in each age group except the group 41 years and over. In women there is a definite upward trend of the mean systolic blood pressure with age. This tendency to increase with

age is not seen in the mean systolic pressures of men (fig. 1). The range in systolic pressure in men was 60 to 229 mm., and in women, 60 to 239 mm.

TABLE 3.—*Diastolic Blood Pressure of Men by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16	114	72.22	72.2	±0.9305	40 to 109
17	1,694	72.65	72.3	±0.2534	20 to 119
18	8,344	72.64	72.1	±0.1136	0 to 129
19	6,470	73.14	72.9	±0.1304	0 to 119
20	5,088	73.14	73.8	±0.1382	0 to 119
21	4,615	74.30	74.8	±0.1411	20 to 129
22	4,105	74.72	75.7	±0.1414	30 to 129
23	3,554	78.17	76.2	±0.1493	0 to 119
24	2,792	80.28	76.3	±0.1646	40 to 119
25	1,934	80.24	76.9	±0.2000	30 to 129
26	1,291	78.18	77.0	±0.2293	50 to 119
27	916	79.39	77.6	±0.2972	40 to 129
28	638	74.68	77.2	±0.3396	50 to 119
29	463	80.84	77.7	±0.4189	50 to 109
30	364	80.59	78.1	±0.4343	50 to 119
31 to 35	853	81.00	77.9	±0.3941	30 to 109
36 to 40	284	78.12	78.1	±0.6890	50 to 119
41 and over	281	80.90	81.4	±0.8725	50 to 119
Total	43,800	74.00	74.5	.....	0 to 129

TABLE 4.—*Diastolic Blood Pressure of Women by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16	159	71.43	67.3	±0.8516	20 to 99
17	2,182	70.80	66.9	±0.2149	20 to 109
18	7,432	70.62	66.6	±0.1217	10 to 109
19	4,753	71.25	68.1	±0.1463	10 to 129
20	4,273	71.66	69.7	±0.1497	10 to 139
21	3,604	72.34	71.6	±0.1493	10 to 119
22	2,786	72.44	72.1	±0.1649	30 to 109
23	1,555	72.60	72.0	±0.2300	20 to 109
24	956	72.65	72.5	±0.2759	40 to 109
25	633	72.83	72.7	±0.3489	40 to 109
26	427	71.80	71.5	±0.4117	40 to 109
27	306	74.20	72.8	±0.5530	40 to 109
28	299	73.57	72.9	±0.5369	40 to 99
29	237	72.88	72.5	±0.5813	40 to 99
30	226	73.12	73.7	±0.5902	50 to 109
31 to 35	820	73.01	74.5	±0.3292	30 to 109
36 to 40	442	77.00	76.2	±0.4367	50 to 109
41 and over	368	81.56	79.4	±0.6612	10 to 139
Total	31,458	71.78	69.7	.....	10 to 139

The mean diastolic pressure in men of all ages was 74.5 mm., and in women, 69.7 mm. At each age the mean diastolic pressure was higher in men than in women. In both men and women there was a tendency for the mean diastolic pressure to increase with age. The range of diastolic blood pressure was from 0 to 129 mm. in men and from 10 to 139 mm. in women (tables 3 and 4).

In order to obtain further information on the effect of age on blood pressure levels, the blood pressure readings were divided into six groups

TABLE 5.—*Percentage Frequency of Systolic Blood Pressure Levels of Men by Age*

Age, Years	Below 100		100 to 109		110 to 119		120 to 129		130 to 139		140 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	7	6.14	20	17.54	30	26.32	38	33.33	15	13.16	4	3.51
17.....	64	3.78	238	14.05	472	27.86	538	31.76	251	14.82	131	7.73
18.....	283	3.39	1,033	12.38	2,323	27.84	2,628	31.50	1,403	16.81	674	8.08
19.....	178	2.75	766	11.84	1,747	27.00	2,100	32.46	1,135	17.54	544	8.41
20.....	120	2.36	534	10.50	1,368	26.89	1,729	33.98	911	17.90	426	8.37
21.....	103	2.23	520	11.27	1,256	27.22	1,583	34.30	783	16.97	370	8.02
22.....	65	1.58	437	10.65	1,136	27.67	1,509	36.76	682	16.61	276	6.72
23.....	57	1.60	373	10.50	955	26.87	1,386	39.00	555	15.62	228	6.42
24.....	43	1.54	309	11.07	783	28.04	1,073	38.43	423	15.15	161	5.77
25.....	28	1.45	220	11.38	572	29.58	726	37.54	275	14.22	113	5.84
26.....	16	1.24	153	11.85	390	30.21	495	38.34	173	13.40	64	4.96
27.....	18	1.97	104	11.35	242	26.42	365	39.85	137	14.96	50	5.46
28.....	8	1.25	79	12.38	189	29.62	262	41.07	72	11.29	28	4.39
29.....	10	2.16	66	14.26	136	29.37	168	36.28	58	12.53	25	5.40
30.....	7	1.92	53	14.56	110	30.22	135	37.09	41	11.26	18	4.94
31 to 35.....	15	1.76	128	15.01	249	29.19	294	34.47	125	14.65	42	4.92
36 to 40.....	5	1.76	51	17.96	97	34.15	77	27.11	34	11.97	20	7.04
41 and over.	5	1.78	37	13.17	83	29.54	82	29.18	45	16.01	29	10.32
All ages.....	1,032	2.36	5,121	11.69	12,138	27.71	15,188	34.68	7,118	16.25	3,203	7.31

TABLE 6.—*Percentage Frequency of Systolic Blood Pressure Levels of Women by Age*

Age, Years	Below 100		100 to 109		110 to 119		120 to 129		130 to 139		140 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	34	21.38	50	31.45	41	25.79	27	16.98	5	3.14	2	1.26
17.....	484	22.18	692	31.71	624	28.60	281	12.88	79	3.62	22	1.01
18.....	1,756	23.63	2,406	32.37	1,960	26.37	970	13.05	269	3.62	71	0.96
19.....	900	18.94	1,509	31.75	1,389	29.22	687	14.45	207	4.36	61	1.28
20.....	644	15.07	1,312	30.70	1,375	32.18	698	16.34	194	4.54	50	1.17
21.....	386	10.71	1,044	28.97	1,300	26.07	695	19.28	140	3.88	39	1.08
22.....	262	9.40	794	28.50	1,011	36.29	567	20.35	123	4.41	29	1.04
23.....	152	9.78	468	30.10	540	34.73	305	19.61	72	4.63	18	1.16
24.....	100	10.46	271	28.35	327	34.20	195	20.40	51	5.33	12	1.26
25.....	60	9.48	186	29.38	218	34.44	130	20.54	31	4.90	8	1.26
26.....	48	11.24	123	28.81	154	36.06	80	18.74	16	3.75	6	1.41
27.....	27	8.82	83	27.12	109	35.62	67	21.90	16	5.23	4	1.31
28.....	28	9.36	83	27.76	96	32.78	63	21.07	21	7.02	6	2.01
29.....	19	8.02	66	27.85	89	37.55	47	19.83	13	5.49	3	1.27
30.....	18	7.96	58	25.66	74	32.74	55	24.34	13	5.75	8	3.54
31 to 35.....	68	8.29	202	24.63	275	33.54	171	20.85	72	8.78	32	3.90
36 to 40.....	30	6.79	101	22.85	137	31.00	112	25.34	47	10.63	15	3.39
41 and over.	10	2.72	59	16.03	83	22.55	95	25.82	62	16.85	59	16.03
All ages.....	5,027	15.98	9,506	30.22	9,804	31.17	5,245	16.67	1,431	4.55	445	1.41

ranging from low to high. The percentage of persons of each age falling into these six groups was computed (tables 5 and 6). For all ages included in the study, 2.36 per cent of the men had a systolic blood pressure below 100 mm., compared with 15.98 per cent of the

women. In the blood pressure range of 100 to 109 mm. were found 11.69 per cent of the men and 30.22 per cent of the women. This tendency for a greater percentage of women than men to have pressures below 109 mm. is seen at each age. The difference is statistically significant for each age group except the group 41 years and over.

Systolic pressures above 120 mm. occurred more frequently in men than in women. In the levels above 130 mm. the percentage frequency was greater in men than in women for each age group except the group

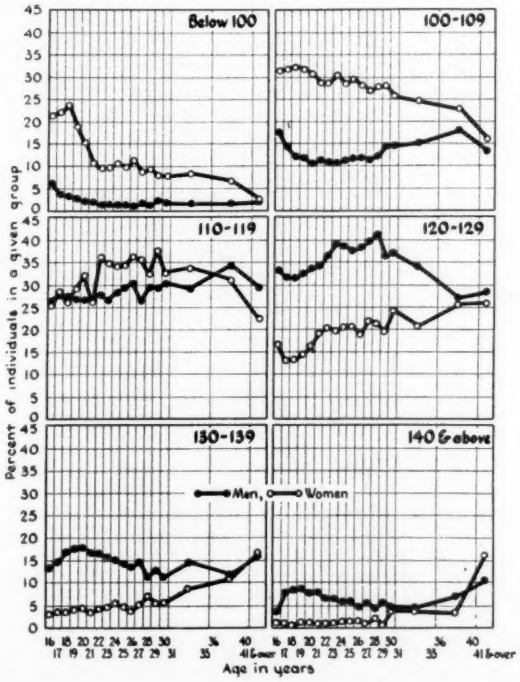

Fig. 2.—Percentage of men and of women in various systolic blood pressure groups.

41 years and over, with the differences statistically significant except in the group aged 16 and the groups 30 years of age and over.

Of the men, 63.39 per cent had systolic readings between 110 and 129 mm. Of the women, however, only 47.84 per cent had systolic pressures between 110 and 129 mm. The majority of the women (61.39 per cent) had systolic pressures between 100 and 119 mm. These age and sex differences are shown graphically in figure 2.

There seems to be little relation between age and systolic pressure levels in men, as shown by the percentage frequency of each age in the

various pressure groups (table 5). It must be kept in mind, however, that over 98 per cent of the men in this study were under 26 years of age. In the women in this study, age and blood pressure seem to be somewhat related, since there was a definitely greater percentage of younger women with pressures below 100 mm. Although the difference is not as striking, there was a tendency for more women in the older age groups than in the younger groups to have pressures above 120 mm. While some of these age differences are statistically significant, the

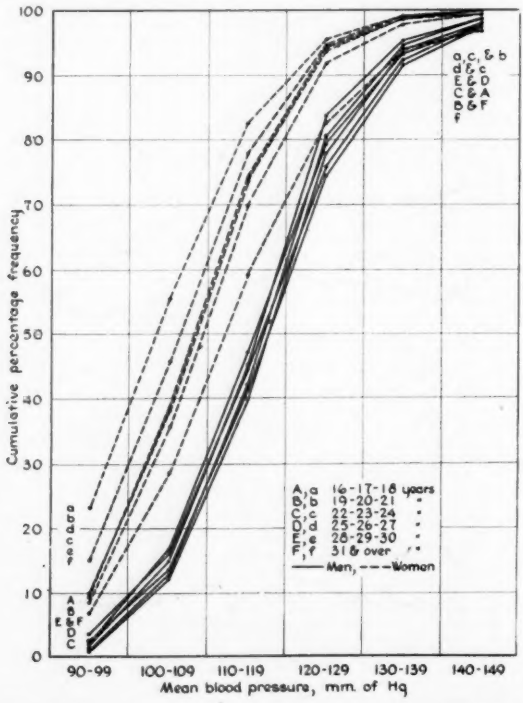

Fig. 3.—Cumulative percentage frequencies of mean systolic blood pressure by age groups and by sex.

trend is not constant. Figure 3 shows the cumulative percentage frequencies of systolic blood pressure levels by age groups and sex which illustrate these age and sex differences.

The tendency for the diastolic blood pressure to increase with age in both men and women, as indicated in tables 3 and 4, is again shown when the percentage frequency of diastolic pressure levels by ages is calculated (tables 7 and 8). With a few exceptions, the differences in diastolic pressure in various age groups are statistically significant in

both men and women. As in the systolic blood pressure, the notable exception to this trend to increase with age is in the age group 41 years and over.

TABLE 7.—*Percentage Frequency of Diastolic Blood Pressure Levels of Men by Age*

Age, Years	0 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	2	1.75	10	8.77	31	27.19	43	37.72	25	21.93	3	2.63
17.....	37	2.18	149	8.80	454	26.80	614	36.25	360	21.25	80	4.72
18.....	180	2.16	773	9.26	2,248	26.94	3,044	36.48	1,719	20.60	380	4.55
19.....	128	1.98	520	8.04	1,605	24.81	2,421	37.42	1,467	22.67	329	5.09
20.....	63	1.24	334	6.56	1,222	24.02	1,940	38.13	1,261	24.78	268	5.27
21.....	44	0.95	236	5.11	978	21.19	1,876	40.65	1,191	25.81	290	6.28
22.....	24	0.58	161	3.92	768	18.71	1,722	41.95	1,164	28.36	266	6.48
23.....	17	0.48	112	3.15	621	17.47	1,513	42.57	1,056	29.71	235	6.61
24.....	9	0.32	86	3.08	508	18.20	1,147	41.08	856	30.66	186	6.66
25.....	6	0.31	46	2.38	321	16.60	812	41.99	599	30.97	150	7.76
26.....	0	0	24	1.86	209	16.19	565	43.76	397	30.75	96	7.44
27.....	3	0.33	19	2.07	129	14.08	388	42.36	297	32.42	80	8.73
28.....	0	0	13	2.04	104	16.30	272	42.63	191	29.94	58	9.09
29.....	0	0	10	2.16	73	15.77	185	39.96	149	32.18	46	9.94
30.....	0	0	5	1.37	49	13.46	151	41.48	127	34.89	32	8.79
31 to 35.....	2	0.23	15	1.76	124	14.54	335	39.27	296	34.70	81	9.50
36 to 40.....	0	0	3	1.06	39	13.73	125	44.01	89	31.34	28	9.86
41 and over.	0	0	2	0.71	24	8.54	102	36.30	102	36.30	51	18.15
All ages.....	515	1.18	2,518	5.75	9,507	21.70	17,255	39.39	11,346	25.90	2,659	6.07

TABLE 8.—*Percentage Frequency of Diastolic Blood Pressure Levels of Women by Age*

Age, Years	0 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	8	5.03	30	18.87	51	32.08	49	30.82	18	11.32	3	1.89
17.....	92	4.21	414	18.97	775	35.52	659	30.20	208	9.53	34	1.56
18.....	393	5.29	1,453	19.55	2,602	35.01	2,127	28.62	728	9.80	129	1.73
19.....	187	3.93	750	15.78	1,610	33.87	1,568	32.99	547	11.51	91	1.91
20.....	121	2.83	508	11.89	1,367	31.99	1,595	37.33	588	13.76	94	2.20
21.....	44	1.22	293	8.13	1,052	29.19	1,497	41.54	636	17.65	82	2.28
22.....	27	0.97	206	7.39	794	28.50	1,186	42.57	494	17.73	79	2.84
23.....	20	1.29	121	7.78	434	27.91	648	41.67	288	18.52	44	2.83
24.....	6	0.63	63	6.59	268	28.03	409	42.78	182	19.04	28	2.93
25.....	5	0.79	39	6.16	173	27.33	272	42.97	124	19.59	20	3.16
26.....	6	1.40	28	6.56	132	30.91	187	43.79	65	15.22	9	2.11
27.....	3	0.98	25	8.17	79	25.82	120	39.22	66	21.57	13	4.25
28.....	3	1.00	26	8.70	69	23.08	126	42.14	62	20.74	13	4.35
29.....	4	1.69	15	6.33	61	25.74	106	44.73	45	18.99	6	2.53
30.....	1	0.44	13	5.75	57	25.22	93	41.15	52	23.01	10	4.43
31 to 35.....	4	0.49	46	5.61	184	22.44	329	40.12	208	25.37	49	5.97
36 to 40.....	1	0.23	14	3.17	88	19.91	178	40.27	126	28.51	35	7.92
41 and over.	1	0.27	12	3.26	59	16.03	117	31.79	119	32.34	60	16.31
All ages.....	926	2.94	4.056	12.89	9,855	31.33	11,266	35.81	4,556	14.48	709	2.54

The sex differences in diastolic pressures followed the same pattern as in the systolic pressures, a much larger percentage of women than men having levels below 70 mm.

SUMMARY

The results of blood pressure determinations on 75,258 persons examined at the Students' Health Service are presented. There were 43,800 men and 31,458 women in the group, most of whom were under 26 years of age.

The mean systolic blood pressure for men of all ages was 122 mm., and for women, 111 mm.

The mean systolic blood pressure of women showed a tendency to rise with age. This trend was not seen in men.

The mean diastolic pressure of men was 74.5 mm. and of women, 69.7 mm.

In both men and women there was a tendency for the diastolic pressure to increase with age.

A greater percentage of women than men had systolic pressures below 109 mm., whereas systolic pressures above 120 mm. occurred more frequently in men except in the age group 41 years and over. Approximately two thirds of the men had systolic pressures between 110 and 129 mm., while about two thirds of the women had systolic pressures between 100 and 119 mm.

The sex differences in diastolic pressures followed the same pattern as in the systolic pressures.

INCIDENCE AND CLINICAL SIGNIFICANCE OF CORONARY ARTERY DISEASE IN DIABETES MELLITUS

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THE INCIDENCE of coronary artery disease in diabetic persons has been investigated repeatedly at autopsy, with general agreement that severe coronary arteriosclerosis is more frequent in the diabetic than in the nondiabetic patient.[1] Of 316 patients with diabetes over the age of 40 included in the report of Root, Bland, Gordon and White,[1a] 38.2 per cent of the men and 32.2 per cent of the women had coronary

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1. (*a*) Root, H. F.; Bland, E. F.; Gordon, W. H., and White, P. D.: Coronary Atherosclerosis in Diabetes Mellitus, J. A. M. A. **113**:27-30 (July 1) 1939. (*b*) Enklewitz, M.: Diabetes and Coronary Thrombosis, Am. Heart J. **9**:386-395 (Feb.) 1934. (*c*) Root, H. F., and Sharkey, T. P.: Coronary Arteriosclerosis in Diabetes Mellitus, New England J. Med. **215**:605-612 (Oct. 1) 1936; (*d*) Arteriosclerosis and Hypertension in Diabetes, Ann. Int. Med. **9**:873-877 (Jan.) 1936. (*e*) Nathanson, M. H.: Coronary Disease in One Hundred Autopsied Diabetics, Am. J. M. Sc. **183**:495-502 (April) 1932. (*f*) Blotner, H.: Coronary Disease in Diabetes Mellitus, New England J. Med. **203**:709-713 (Oct. 9) 1930. (*g*) Gibb, W. F., and Logan, V. W.: Diabetes Mellitus: A Study of One Hundred and Forty-Seven Autopsied Diabetics, Arch. Int. Med. **43**:376-383 (March) 1929. (*h*) Warren, S.: The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1938. (*i*) Wilder, R. M.: Clinical Diabetes and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1941; Diabetic Arteriosclerosis (Henry Sewall Lecture), Internat. Clin. **2**:13-30 (June) 1939. (*j*) Lisa, J. R.; Magiday, M.; Galloway, I., and Hart, J. F.: Arteriosclerosis with Diabetes Mellitus, J. A. M. A. **120**:192-195 (Sept. 19) 1942.

artery occlusions. The same study demonstrated such occlusions in only 9.9 per cent of 1,521 nondiabetic men and in 4.9 per cent of 789 nondiabetic women, all over the age of 40. In the same age group Enklewitz [1b] found coronary artery occlusions in 31.8 per cent of 261 persons with diabetes.

In the hearts of a group of unselected patients studied by an improved technic of injection plus dissection for the detection of pathologic alterations in the coronary arteries,[2] one of us has found that arterial occlusions were almost as frequent as in previously reported series of diabetic hearts studied by routine methods.[3] Included in a consecutive series of 643 hearts studied by this improved technic were 54 (8.4 per cent) from patients with a clinical diagnosis of diabetes mellitus. Because their glycosuria was discovered only during the terminal illness, 4 of these patients were not considered to have proved diabetes. The diagnosis of diabetes mellitus in the remaining 50 patients was based on adequate history and laboratory evidence, and their hearts were made the basis of an analysis of the relationship of diabetes to coronary heart disease.

FUNCTIONALLY SIGNIFICANT CORONARY ARTERIOSCLEROSIS

The coronary artery tree of every one of the 50 diabetic hearts showed some arteriosclerosis. Six of the diabetic hearts showed so little that no note of coronary artery narrowing was made during the dissection of the injected vessels and no narrowing was detectible in the roentgenogram of the injected coronary artery tree. These 6 hearts were considered to show 0 to 1 plus coronary arteriosclerosis (table 1). At the other extreme were 28 diabetic hearts containing one or more points of arterial narrowing and one or more old complete arterial occlusions which antedated the terminal illness. These were considered to show 4 plus coronary arteriosclerosis.

The remaining 16 hearts showed an intermediate degree of coronary arteriosclerosis. Dissection showed definite narrowing of the lumen at one or more points of the coronary artery tree but no arterial occlusion. Rather than rely entirely on this purely subjective impression of the degree and extent of arterial narrowing, the collateral evidence of myocardial fibrosis and of intercoronary anastomosis was utilized to evaluate the functional significance of narrowing of the coronary arteries. The degree of myocardial fibrosis may be considered an objective anatomic measure of the functional significance of coronary arteriosclerosis in the absence of other etiologic factors. For the purposes of this evaluation, myocardial fibrosis was accepted as present only when there was definite

2. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, Am. Heart J. **15**:528-568 (May) 1938.

3. Schlesinger, M. J., and Zoll, P. M.: Incidence and Localization of Coronary Artery Occlusions, Arch. Path. **32**:178-188 (Aug.) 1941.

scarring of the ventricular muscle in regions other than the annulus fibrosus of the valves, the tips of the papillary muscles or the immediate vicinity of the blood vessels.

Such myocardial fibrosis was found in all 28 diabetic hearts with old coronary artery occlusions and narrowings. In contrast (table 1), the 6 diabetic hearts without narrowed coronary arteries showed no such fibrosis. Nine of the 16 intermediate hearts with narrowed arteries without complete occlusions showed myocardial fibrosis. These 9 hearts were therefore considered to have 3 plus coronary arteriosclerosis. The remaining 7 hearts, with narrowed arteries but no fibrosis, were graded as presenting 2 plus coronary arteriosclerosis.

Intercoronary anastomoses have also been considered to be a compensatory sequel to the development of significant coronary artery narrowing, although such anastomoses also occur in a small percentage of normal hearts.[2] In this series, all 28 hearts with old arterial occlusions and narrowings and myocardial fibrosis exhibited intercoronary anastomoses

TABLE 1.—*Functional Significance of Coronary Arteriosclerosis*

Degree of Sclerosis	No. of Hearts	Arterial Narrowings	Old Arterial Occlusions	Myocardial Fibrosis	Anastomoses	Functional Significance
0 to 1+	6	0	0	0	0	Not functionally significant (13)
2+	4	+	0	0	0	
	3	+	0	0	+	
3+	3	+	0	+	0	Functionally significant (37)
	6	+	0	+	+	
4+	28	+	+	+	+	

as well. The 6 hearts without such occlusions, narrowings or fibrosis showed no anastomoses. In the intermediate group, anastomoses were slightly more frequent in the hearts showing fibrosis (3 plus coronary arteriosclerosis) than in those in which the myocardium was not thus affected (2 plus arteriosclerosis). As thus differentiated, 3 plus and 4 plus coronary arteriosclerosis was considered to have been functionally significant during life and 1 plus to 2 plus sclerosis to have been of lesser functional significance.

Degree of Coronary Arteriosclerosis in Hearts of Diabetic and Nondiabetic Patients.—The average age of the 50 diabetic patients was 64.7 years; none was less than 42 years old at the time of death. The nondiabetic control series of hearts was therefore restricted to those from 400 consecutive and contemporary patients over the age of 40. The average age of the control group was 61.1 years. As in other studies,[1a, c] women predominated among the 50 diabetic patients, only 19 (38 per cent) of whom were men. Among the controls were 255 (64 per cent) men and 145 (36 per cent) women.

The degree of coronary arteriosclerosis in these two groups is indicated in table 2. Functionally significant coronary arteriosclerosis

occurred in 37 (74 per cent) of the 50 diabetic patients but in only 149 (37 per cent) of the 400 controls. The relative immunity of nondiabetic women to severe coronary artery disease was striking, although male and female diabetic patients were equally affected. Old coronary artery occlusions were present in 55 per cent of the diabetic women but in only 6 per cent of the nondiabetic women.

If fresh as well as old arterial occlusions are taken into consideration, the difference between hearts from diabetic patients and those from

TABLE 2.—*Degree of Coronary Arteriosclerosis in Diabetic and Nondiabetic Patients Over the Age of 40*

Degree of Sclerosis	50 Diabetic Patients						400 Nondiabetic Patients					
	Male		Female		Total		Male		Female		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Not functionally significant												
1+	1	5	5	16	6	12	97	38	101	70	198	50
2+	3	16	4	13	7	14	40	16	13	9	53	13
Functionally significant												
3+	4	21	5	16	9	18	51	20	22	15	73	18
4+	11	58	17	55	28	56	67	26	9	6	76	19
Totals.....	19	100	31	100	50	100	255	100	145	100	400	100

TABLE 3.—*Incidence of Coronary Artery Occlusions in Hearts of Diabetic and Nondiabetic Patients*

Type of Occlusion	Diabetic Patients			Nondiabetic Patients		
	Men (19)	Women (31)	Total (50)	Men (255)	Women (145)	Total (400)
Old.....	7	11	18	48	6	54
Fresh.....	2	2	4	15	2	17
Fresh and old.....	4	6	10	15	3	18
Total.....	13 (68%)	19 (61%)	32 (64%)	78 (31%)	11 (8%)	89 (23%)

nondiabetic patients is even more marked (table 3). Old or fresh arterial occlusions were found in 32 (64 per cent) of the 50 diabetic hearts and as frequently in women as in men. In 18 of these 32 hearts the occlusions were old, in 4 they were fresh and in 10 they were both fresh and old. Similar occlusions, however, were found in only 23 per cent of the controls, occurring in 31 per cent of the nondiabetic men and in but 8 per cent of the nondiabetic women. Thus, diabetic persons are twice as likely to have coronary artery occlusions as are nondiabetic men and eight times as likely as are nondiabetic women.

Angina Pectoris.—Various observers have reported on the incidence of angina pectoris in diabetes. Wilder [11] considered angina pectoris uncommon in persons with diabetes except in association with an

occlusive episode of coronary artery disease. Rabinowitch, Ritchie and McKee [4] found only 19 patients (1.3 per cent) with this condition in a group of 1,500 patients with diabetes. Root and Graybiel [5] encountered but 210 patients (3 per cent) with angina pectoris among 7,000 diabetic persons of all ages. On the other hand, Edeiken [6] observed angina pectoris in 8 per cent and thoracic pain of uncertain origin in another 5 per cent of a group of 100 diabetic patients unselected as to age, while Friedman [7] made the diagnosis of angina pectoris in 9 per cent of a large group of diabetic persons over the age of 40. The low incidence of angina pectoris reported by these observers in patients who are known to have a high incidence of severe coronary artery disease seems inconsistent.

For the purpose of this report, the clinical records of all 450 patients were reviewed, and the diagnosis of angina pectoris was accepted only on the basis of "a syndrome consisting of paroxysmal substernal or

TABLE 4.—*Incidence of Angina Pectoris in Diabetic and Nondiabetic Patients*

Degree of Sclerosis	1+ to 2+ Not Functionally Significant		3+ to 4+ Functionally Significant		Total	
	Angina	No Angina	Angina	No Angina	Angina	No Angina
Diabetic						
Male (19)	0	4	6	9	6	13
Female (31)	1	8	7	15	8	23
Total (50)	1	12	13	24	14	36
Nondiabetic						
Male (255)	4	133	46	72	50	205
Female (145)	3	111	6	25	9	136
Total (400)	7	244	52	97	59	341

precordial pain or discomfort of short duration, not infrequently radiating to the shoulders and inner aspect of the arms, precipitated by exertion, emotion or other states in which the work of the heart is increased and relieved by rest or nitroglycerin." [8]

Angina pectoris thus defined was diagnosed, with no significant sex difference (table 4), in 14 (28 per cent) of the 50 diabetic patients and

4. Rabinowitch, I. M.; Ritchie, W. L., and McKee, S. H.: A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus, Ann. Int. Med. **7**:1478-1490 (June) 1934.

5. Root, H. F., and Graybiel, A. J.: Angina Pectoris and Diabetes Mellitus, J. A. M. A. **96**:925-928 (March 21) 1931.

6. Edeiken, J.: Diabetes Mellitus as Observed in One Hundred Cases for Ten or More Years: II. Cardiac Studies, Am. J. M. Sc. **209**:8-16 (Jan.) 1945.

7. Friedman, G.: Cardiovascular Status of Diabetic Patients After the Fourth Decade of Life, Arch. Int. Med. **55**:371-394 (March) 1935.

8. Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis and Myocardial Infarction to the Pathologic Findings, Am. Heart J. **19**:1-91 (Jan.) 1940.

in 59 (15 per cent) of the 400 nondiabetic patients. Only 1 of the diabetic patients with angina pectoris did not have functionally significant coronary arteriosclerosis.[9] One third of both the 37 diabetic and the 149 nondiabetic patients with functionally significant coronary arteriosclerosis had had angina pectoris. Consistent with their higher incidence of functionally significant coronary arteriosclerosis, both men and women with diabetes show a higher incidence of angina pectoris than do those without diabetes. The relative infrequency of angina pectoris in nondiabetic women over 40 years of age is striking.

The frequency with which angina pectoris was found in this series of patients is probably due to the special interest of our associates in coronary artery disease. Patients often do not volunteer symptoms which suggest the diagnosis of angina pectoris, particularly when the discomfort is mild. The frequency with which angina pectoris is discovered depends partly on the direct attempt of the physician to elicit a characteristic history.

Fresh Coronary Thrombotic Occlusion and Cardiac Infarction.—Because of the high incidence of functionally significant coronary arteriosclerosis and of angina pectoris among diabetic patients, a parallel frequency of cardiac infarction might be expected. Warren,[1b] however, found only forty-one fresh infarcts and 10 instances of "coronary thrombosis without infarction" at autopsy on 440 diabetic patients of all age groups, an incidence of but 11.6 per cent. Beardwood[10] reported that only 240 deaths (15 per cent) were attributable to coronary artery disease among the 1,579 patients with diabetes who died in Philadelphia during the years 1940 to 1942. However, Pollack, Dolger and Ellenberg[11] encountered "acute coronary thrombosis" in 20.4 per cent of 113 diabetic patients, unselected as to age, at autopsy. Among 87 patients with diabetes over the age of 40, Enklewitz[1b] demonstrated "coronary thrombosis" with or without infarction in 29.8 per cent, and a 30 per cent incidence of cardiac infarction in a series of 193 such patients was reported by Lisa, Magiday, Galloway and Hart.[1j]

In the present series, none of the 13 diabetic patients with hearts free from functionally significant coronary arteriosclerosis died with the clinical picture of acute cardiac infarction. Also, none of their hearts had a fresh coronary thrombotic occlusion or a cardiac infarct. However, 14 (38 per cent) of the 37 hearts from diabetic persons with

9. This was a 66 year old hypertensive woman with hemolytic anemia.

10. Beardwood, J. T.: Report of Diabetic Surveys in Philadelphia: Analysis of 1,579 Deaths in Diabetics in Philadelphia 1940-1942, Proc. New York Diabetes A. **11**:345-355 (Feb.) 1944.

11. Pollack, H.; Dolger, H. A., and Ellenberg, M.: An Analysis of the Diabetic Morbidity and Mortality in a General Hospital, Am. J. M. Sc. **202**:246-251 (Aug.) 1941.

functionally significant coronary arteriosclerosis showed fresh cardiac infarcts at autopsy (table 5). Only 9 of these hearts had fresh coronary thrombotic occlusions. Four exhibited old arterial occlusions only and 1 arterial narrowings only. In 8 instances, old occlusions accompanied the fresh thrombotic occlusions.

These 14 hearts did not represent the total mortality in the diabetic group directly due to acute coronary artery disease. In 3 additional patients with functionally significant coronary arteriosclerosis, the interval between the onset of clinical symptoms of acute coronary failure and the time of death was too short to permit the development of a recognizable infarct. In each of these 3 hearts multiple old arterial occlusions and narrowings were present, and in 1 of them there was also a fresh thrombotic occlusion.

TABLE 5.—*Death from Coronary Heart Disease in Patients with Functionally Significant Coronary Arteriosclerosis*

	Diabetic Patients (37)			Nondiabetic Patients (149)		
	Coronary Deaths (17)			Coronary Deaths (55)		
	With Fresh Infaret	Without Fresh Infaret	Noncoronary Deaths (20)	With Fresh Infaret	Without Fresh Infaret	Noncoronary Deaths (94)
Old occlusions	4	2	12	15	6	33
Fresh thrombotic occlusions	1	0	3	13	2	2
Fresh thrombotic and old occlusions	8	1	1	9	3	6
No occlusions	1	0	4	6	1	53
Total	14	3	20	43	12	94

The demonstration of a fresh thrombotic occlusion in a coronary artery tree does not of itself warrant the presumption that death was due to acute coronary failure. Such fresh thrombotic occlusions may occur terminally as a result of vascular collapse, with slowing of blood flow in the coronary arteries.[12] They do not necessarily cause symptoms or death. Four of the patients whose hearts showed fresh thrombotic occlusions without fresh infarction did not present the terminal clinical picture of acute coronary failure and their deaths were therefore not included as attributable to that condition.

In summary, 17 (34 per cent) of the entire group of 50 diabetic patients died with the clinical syndrome of acute coronary heart disease. In the control group of 400 nondiabetic patients, an identical analysis revealed the incidence of death from acute coronary heart disease to be only 14 per cent (table 5).

12. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock, Arch. Int. Med. **68**:181-198 (Aug.) 1941.

RELATIONSHIP OF HYPERTENSION TO CORONARY ARTERY DISEASE IN DIABETIC PATIENTS

Hypertension was found by Root and Sharkey [1c] in 53.1 per cent of 175 patients with diabetes of all age groups; it was found by Enklewitz [1b] in 44 per cent and by Friedman [7] in 46 per cent of diabetic persons over the age of 40. In diabetic [1c] as well as in nondiabetic patients hypertension is thought to intensify the effects of coronary artery disease. The high incidence (74 per cent) of hypertension in our 50 diabetic men and women may be related to the high incidence of significant coronary artery disease in this series.

The diagnosis of hypertension was made in the patients in this series on the basis of recorded blood pressure readings of more than 150 mm.

TABLE 6.—*Relation of Hypertension to Heart Disease in Diabetic Patients*

	Nonhypertensive Patients (13)	Hypertensive Patients (37)
Deaths from acute coronary disease	2 (15%)	15 (41%)
Congestive heart failure	5 (38%)	22 (60%)
Myocardial fibrosis	5 (38%)	24 (65%)
Fresh or old cardiac infarct	0	18 (49%)

TABLE 7.—*Relation of Severity of Diabetes to Degree of Coronary Arteriosclerosis*

Severity of Diabetes	Coronary Arteriosclerosis: Not Functionally Significant	Coronary Arteriosclerosis: Functionally Significant	Totals
Mild (no insulin)	6	16	22
Moderate (1 to 20 units of insulin daily)	3	10	13
Severe (more than 20 units of insulin per day)	2	11	13
Total	11	37	48

of mercury systolic and of 90 mm. of mercury or more diastolic. In the few instances in which the hospital record of the terminal illness constituted our only recorded data, previous blood pressure readings were obtained from the family physician or from other hospitals.

As indicated in table 6, not only do hypertensive diabetic patients die more frequently from acute coronary heart disease than do the nonhypertensive but also congestive heart failure develops in them more often. The hearts of the hypertensive group more frequently exhibited diffuse myocardial fibrosis or actual myocardial infarction.

RELATIONSHIP OF SEVERITY AND DURATION OF DIABETES TO SEVERITY OF CORONARY ARTERIOSCLEROSIS

In 48 of the diabetic patients the data were sufficiently complete for estimation of the severity of the disease as judged by the amount of

insulin used (table 7). No definite correlation between the severity of the diabetes and the severity of coronary arteriosclerosis was found.

However, there was a direct relationship between the degree of such sclerosis and the duration of the diabetes (table 8). The known duration of the diabetes could be determined from the histories of 47 patients. The average duration of diabetes at the time of death in 36 patients with functionally significant coronary arteriosclerosis was almost twice the average duration of the disease in 11 patients whose coronary artery disease was not functionally significant. Since the average age of the two groups was approximately the same, this disproportion could not be explained on the basis of a difference in age.

Thus, the well established observation [13] that the severity of coronary arteriosclerosis is more closely related to the duration than to the

TABLE 8.—*Relation of Duration of Diabetes to Severity of Coronary Arteriosclerosis*

	Coronary Arteriosclerosis Not Functionally Significant			Coronary Arteriosclerosis Functionally Significant		
	No. of Cases	Average Age, Yr.	Average Duration of Diabetes, Yr.	No. of Cases	Average Age, Yr.	Average Duration of Diabetes, Yr.
Male	3	67.0	5.3	14	64.3	11.2
Female	8	66.4	5.9	22	63.4	10.0
Total	11	66.6	5.7	36	63.9	10.5

severity of the diabetes is confirmed in this group of patients in which a high incidence of coronary artery disease was discovered.

COMMENT

Although advanced coronary artery disease is generally accepted as a frequent complication of diabetes, the high incidence of this complication has not been fully appreciated. In small part this has been due to the statistical inclusion of young persons with diabetes, in whom severe coronary artery disease, although not rare,[1h] is relatively infrequent. Of approximately 1,000,000 persons with diabetes in the United States, 25 per cent are estimated to be less than 44 years of age.[14] The inclusion of these in any survey of coronary heart disease would tend to minimize the frequency with which this complication contributes to the morbidity and mortality of older diabetic patients.

A second factor is the survival of diabetic persons to ages at which coronary artery disease becomes more frequent and more severe even in persons without diabetes. Thus, the average age at death of persons

13. Root and others.[1a] Root and Sharkey.[1c] Rabinowitch and others.[4] Root and Graybiel.[5]

14. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946.

with diabetes has gradually risen from 44.5 years in 1898 to 64.5 years in 1945.[14]

Perhaps the most important factor in the underestimation of the severity of coronary heart disease in diabetic patients is the imperfection of routine methods of postmortem examination of the arteries. Occlusions have been demonstrated twice as frequently in such patients by the injection plus dissection technic as by previously reported conventional methods of examining the larger coronary arteries.[8] Moreover, the use of this improved method, combined with the microscopic examination of the myocardium, makes it possible to establish rational criteria for estimating the functional significance of the coronary artery disease in a given heart.

The present study, utilizing the improved technic, demonstrated that at the time of death functionally significant coronary artery disease was present in approximately three fourths of our diabetic patients. In one third of the entire group the cause of death was acute coronary heart disease, and one quarter of the patients had had angina pectoris during life.

This high morbidity cannot be explained by the predominance of a particular racial group in this series. When studied by routine pathologic technics in both institutions, the incidence of coronary occlusions in a predominantly non-Jewish population at the Massachusetts General Hospital was 11.0 per cent, as compared to a 10.5 per cent incidence in the predominantly Jewish population at the Beth Israel Hospital.[3] However, it is possible that the high incidence of functionally significant coronary heart disease in this series of diabetic patients is related to the high incidence of hypertension in the group.

In middle-aged persons with diabetes the clinical diagnosis of functionally significant coronary artery disease can be made more frequently by maintaining a high index of suspicion, obtaining a careful history and performing proper clinical and laboratory studies. Any diabetic man or woman over the age of 40 can be assumed to have advanced coronary artery disease even in the absence of symptoms, particularly if hypertension is present, and more particularly if the diabetes is of more than ten years' duration. Pain in the chest in a middle-aged diabetic patient should be considered as angina pectoris due to coronary heart disease unless some other disease can be shown to be the definite and sole cause of the complaint. On the other hand, absence of complaints suggestive of angina pectoris does not militate against the application of this general rule, inasmuch as it has been shown that angina pectoris often does not occur until multiple coronary artery occlusions and narrowings have already developed.[8]

In the absence of precise knowledge concerning the cause of arteriosclerosis, prevention of coronary artery disease is not now possible.

Early detection of symptoms due to this complication in the patient with diabetes, however, should lead to the early institution of a regimen designed to avoid or postpone so far as possible the onset of the sequelae of coronary arteriosclerosis.

The proper use of insulin is important in this respect, since insulin hypoglycemia, by causing stimulation of the sympathetic nervous system and the discharge of epinephrine,[15] greatly increases cardiac work.[16] By this mechanism, hypoglycemia may precipitate angina pectoris or even myocardial infarction. "Knife-edge" control of the blood sugar level in diabetic patients is therefore undesirable in the presence of coronary artery disease, since neither the activity nor the diet of most patients can be controlled continuously and with exactitude. Rather than risk hypoglycemia, therefore, it seems wiser to regulate the middle-aged or elderly diabetic patient so as to maintain the fasting blood sugar level at not less than 120 mg. per hundred cubic centimeters. In the absence of diabetic symptoms, ketonuria and loss of weight, such a constant mild hyperglycemia is preferable to a more rigid type of control which sooner or later will be complicated by insulin hypoglycemia.

It is doubtful whether such a control of diabetes will accelerate the rate of progression of coronary arteriosclerosis, since the severity of the diabetes, at least as measured by insulin requirement, has little relation to the degree of coronary arteriosclerosis. Furthermore, no correlation can be shown to exist in uncomplicated diabetes between the level of the blood sugar and hyperlipemia, since even in instances of poorly regulated diabetes the blood lipids may be within the normal range.[17]

SUMMARY AND CONCLUSIONS

Functionally significant coronary artery disease was disclosed in approximately three fourths of the hearts of 50 diabetic patients by means of postmortem injection plus dissection technic. One third of these patients had died of acute coronary heart disease. One quarter of the entire group had had angina pectoris.

Among diabetic women over the age of 40 the incidence of significant coronary arteriosclerosis, of angina pectoris and of death due to coronary artery disease is as great as among diabetic men. This is in

15. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on the Condition of Activity in Endocrine Glands: XIII. A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46-66 (June) 1924.

16. Ernestene, A. C., and Altschule, M. D.: The Effect of Insulin Hypoglycemia on the Circulation, J. Clin. Investigation **10**:521-528 (Aug.) 1931.

17. Man, E. B., and Peters, J. P.: Serum Lipoids in Diabetes, J. Clin. Investigation **14**:579-594 (Sept.) 1935. Chaikoff, I. L.; Smyth, F. S., and Gibbs, G. E.: The Blood Lipoids of Diabetic Children, ibid. **15**:627-631 (Nov.) 1936.

sharp distinction to the sex difference in these respects in the nondiabetic population.

Angina pectoris, deaths due to acute coronary disease and congestive heart failure all are more common when hypertension is present in diabetic patients than than when the blood pressure is normal.

The severity of the coronary arteriosclerosis is correlated with the duration but not with the severity of the diabetes.

Early detection of the symptoms of coronary artery disease in persons with diabetes is necessary if the sequelae of coronary arteriosclerosis are to be postponed or avoided.

Mild hyperglycemia is preferable to a regimen which may result in insulin hypoglycemia and the attendant risk of precipitating myocardial infarction.

MARFAN'S SYNDROME IN THE ADULT

Dissecting Aneurysm of the Aorta Associated with Arachnodactyly

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ARACHNODACTYLY (Marfan's syndrome) is a relatively rare familial symptom complex which is familiar to ophthalmologists, pediatricians and, to a lesser extent, orthopedic surgeons. It should be of interest to all physicians. We wish to summarize its important characteristics and emphasize the aortic lesions which may be associated with it.

REVIEW OF THE LITERATURE

Although entitled dolichostenomelie by Marfan,[1] Archard[2] in 1902 emphasized the most characteristic feature of the syndrome, calling it arachnodactyly (spider fingers). In 1926 Piper and Irving-Jones,[3] the first American physicians to record the condition, noted the frequency with which it is associated with congenital malformations of the heart. Futcher and Southworth[4] in 1938 pointed out rheumatic endocarditis and pulmonary disorders as common medical complications. In 1943 Baer, Taussig and Oppenheimer[5] reported 2 cases in which aneurysmal

From the Departments of Medicine and Pathology, University of Chicago Clinics.

1. Marfan, A. B.: Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220-226 (Feb. 28) 1896.

2. Achard, C.: Arachnodactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834-840 (Oct. 10) 1902.

3. Piper, R. K., and Irving-Jones, E.: Arachnodactylia and Its Association with Congenital Heart Diease, Am. J. Dis. Child. **31**:832-839 (June) 1926.

4. Futcher, P. H., and Southworth, H.: Arachnodactyly and Its Medical Complications, Arch. Int. Med **61**:693-703 (May) 1938.

5. Baer, R. W.; Taussig, H. B., and Oppenheimer, E. H.: Congenital Aneurysmal Dilatation of the Aorta Associated with Arachnodactyly, Bull. Johns Hopkins Hosp. **72**:309-317 (June) 1943.

dilatation of the aorta was found at autopsy. The same year Etter and Glover [6] described a case in which death resulted from dissecting aneurysm of the aorta. Parker and Hare [7] in 1945 demonstrated roentgenologic evidence of aneurysmal dilatation of the aorta in a patient with arachnodactyly. A comprehensive review of the literature was published by Rados [8] in 1942.

The diagnosis of arachnodactyly can usually be established by inspection if the examiner is familiar with the condition. In the majority of the cases the skull is dolichocephalic. The supraorbital ridges are prominent. There is bossing of the frontal eminences, and the eyes are sunken. The auricles of the ears are large and protruding, and the jaw juts forward. The teeth are long, narrow and irregularly spaced. The palate is high, arched, narrow and frequently cleft. These features, coupled with the fact that the wearing of glasses is a necessity for the majority of patients with this disease, tend to endow them with a serious, prematurely aged appearance. The limbs are exceedingly long and slender. The span between the tips of the middle fingers with the arms extended often is greater than the length. The metacarpal bones and the phalanges, especially the terminal phalanges, are increased in length, giving the fingers a delicate, spider-like appearance. The metatarsal bones and the toes are also long and slender. This slenderness and delicacy of the limbs, hands and feet are enhanced by the meager amount of subcutaneous fat and the poorly developed, hypotonic musculature. These abnormalities tend to give the general impression of emaciation. Laxity of ligamentous structures permits hypermobility of joints and may be marked enough to allow subluxation. The laxity of ligaments and the inadequate muscular development are believed to be the primary cause of the frequent spinal and thoracic deformities which do not appear until a child with this syndrome begins to walk. The spinal deformities are kyphosis and scoliosis; the thoracic deformity is usually characterized by a funnel chest, but pigeon breast, with narrowness and flattening of the thoracic wall, may be seen. Contractures, spurring of the os calcis, pes planus, hammer toes, club foot and spina bifida occulta are other not uncommon deformities.

The ocular defect is characteristic. This consists in congenital bilateral dislocation of the lenses. The iris, being unsupported by the lens, shows tremulousness (iridodonesis) when the head is moved from

6. Etter, L. E., and Glover, L. P.: Arachnodactyly Complicated by Dislocated Lens and Death from Rupture of Dissecting Aneurysm of Aorta, J. A. M. A. **123**:88-89 (Sept. 11) 1943.

7. Parker, A. S., Jr., and Hare, H. F.: Arachnodactyly, Radiology **45**:220-226 (Sept.) 1945.

8. Rados, A.: Marfan's Syndrome (Arachnodactyly Coupled with Dislocation of Lens), Arch. Ophth. **27**:477-538 (March) 1942.

side to side. Myopia is the rule, and vision is seriously impaired. The pupils are small, and the response to atropine is feeble.

The presence of a cardiac abnormality, congenital or acquired, is most common in arachnodactyly, and it is of interest that there is usually a paucity of symptoms in the presence of definitive clinical signs. The signs necessarily vary with the particular disorder. Roentgenograms of the chest may reveal cardiac enlargement, but their interpretation is commonly difficult because of thoracic deformities.

Congenital malformations of the lungs are frequent and, combined with thoracic deformity, make pulmonary disease a dangerous complication. Pneumonia is a particularly common cause of death.

All these abnormalities may be present in a single case; however, as a rule one or more will be missing. The presence of the commonest characteristics is sufficient for the diagnosis.

Heredity.—Formes frustes, with stigmas of the disease, may be noted among the siblings of a person with typical arachnodactyly. Young [9] has described a brother and sister with ectopia lentis and arachnodactyly. Weve [10] has published reports of a father with dislocations of the lenses who had sixteen children. Five of these died; four were believed to have had arachnodactyly. Of the eleven living children, three (two boys and a girl) had the characteristic habitus. Weve's second family consisted of a father, two sons and a daughter. All had the typical manifestations of the syndrome, and their paternal grandfather was said to have been similarly afflicted.

Sex.—Rados [8] reviewed 204 cases, involving 101 males and 103 females.

Race.—Almost all the patients about whom case reports have been written are white, but arachnodactyly has been reported in Negroes by Futcher and Southworth,[4] Rambar and Denenholz,[11] and Baer, Taussig and Oppenheimer.[5]

Etiologic Factors.—The syndrome is of unknown origin, but many theories have been proposed. Salle [12] considered arachnodactyly to be the result of pituitary dysfunction and related to giantism and acromegaly. Weve [10] emphasized the part played by fetal disturbance in mesodermal structures, but other authors have pointed out that some of the typical ocular findings are primarily the result of abnormalities

9. Young, M. L.: Arachnodactyly, Arch. Dis. Childhood **4**:190-214 (Aug.) 1929.

10. Weve, H.: Ueber Arachnodaktylie, Arch. f. Augenh. **104**:1-46 (May) 1931.

11. Rambar, A. C., and Denenholz, E. J.: Arachnodactyly, J. Pediat. **15**:844-852 (Dec.) 1939.

12. Salle, V.: Ueber einem Fall von angeborener abnormer Grösse der Extremitäten, Jahrb. f. Kinderh. **75**:540-550, 1912.

Postmortem Findings in Twelve Cases of Arachnodactyly

Author	Sex and Age at Death	Anatomic Findings (Not Related to Heart and Aorta)	Heart and Aorta
Bergstrand [10]	Female 19 days (premature)	Monolobed left lung; bronchopneumonia; microscopic: questionable increase in eosinophil cells in pars anterior of the hypophysis	Normal heart
Salle [12]	Male 2½ mo.	Enlargement of the sella turcica; slight enlargement of the pituitary; exostosis of the sella; abnormal elongation of the intestines; microscopic: increase in eosinophil cells in pars anterior of the hypophysis	Dilatation of the heart; hypertrophy of the heart; patent foramen ovale (gray-red nodulations were noted along the margins of the tricuspid and aortic valves)
Börger [16]	Female 1 yr.	Vestigial middle lobe of the right lung; abnormal enlargement of the lingula of the left lung; bronchopneumonia; microscopic: increase in eosinophil cells in pars anterior and cysts in pars intermedia of the hypophysis	Patent foramen ovale; heart of normal size and shape
Piper and Irving-Jones [3]	Female 21 mo.	Monolobed left lung and vestigial middle lobe of the right lung; normal hypophysis	Hypertrophy of the heart; interauricular septal defect
Rambar and Denenholz [11]	Male 27½ mo.	Bronchopneumonia; absence of the dilator pupillae bilaterally; normal hypophysis	Normal heart
Apert, E.: Nourrisson **26**: 1-12 (Jan.) 1938	Female 13 yr.	Atherosclerosis of the pulmonary artery; vestigial middle lobe of the right lung	Hypertrophy of the right ventricle; patent ductus botalli
Baer, Taussig and Oppenheimer [5]	Female 14 yr.	None *	Hypertrophic heart (560 Gm.); patent foramen ovale; wrinkling and nodulation of mitral valve; Macallum patch; dilatation of aortic orifice; displacement of coronary ostia upward; aneurysmal dilatation of the ascending aorta; congenital malformation of the aortic media; no evidence of old rheumatic activity
Olcott, C. T.: Am. J. Dis. Child. **60**: 660-668 (Sept.) 1940	Female 16 yr.	Bronchopneumonia; cysts in the thyroid and in the pars intermedia of the hypophysis; hypoplasia of the uterus and ovaries; microscopic: round cell infiltration of the gastric mucosa	Hypertrophic heart (520 Gm.); fenestration of the posterior cusp of the mitral valve and calcification and nodular thickening of the mitral valve ring; acute vegetative endocarditis
Etter and Glover [9]	Male 21 yr.	None *	Incomplete report stated: "aortic valvular regurgitation with pronounced myocardial hypertrophy and massive hemopericardium; chronic dissecting aneurysm of the ascending aorta with fatal rupture into pericardium"
Baer, Taussig and Oppenheimer [5]	Male 25 yr.	Passive congestion of the liver; normal hypophysis	Hypertrophic heart (840 Gm.); dilatation of the heart; patent foramen ovale; thickening of the endocardium beneath the aortic valve; dilatation of the aortic orifice; aneurysmal dilatation of the ascending aorta; displacement of the coronary ostia upward; congenital malformation of the aortic media; no evidence of old rheumatic activity
Weill [15]	Female 27 yr.	Microscopic: increase in eosinophil cells in pars anterior of the hypophysis	Dilated hypertrophic heart (490 Gm.); marked dilatation of the aortic orifice; fusion and thickening of the left and posterior aortic valve cusps; dilatation of the intrapericardial portion of the aorta, with saclike ectasia of the sinuses of Valsalva; healed endocarditis
Weill [15]	Male 47 yr.	Enlarged thymus; defect in falx cerebri; symphysis of the frontal lobes; normal hypophysis	Heart of normal size and shape; yellowish thickening of gelatinous consistency covered the "free face" of the mitral valve; healed endocarditis or mucous degeneration

* The postmortem record on these patients was incomplete.

affecting ectodermal structures. Passow [13] considered the condition to be closely related to status dysraphicus or to microform syringomyelia, which has some features similar to those of arachnodactyly.

Summary of Postmortem Examinations.—Although over 200 cases of arachnodactyly have been reported, descriptions of only twelve autopsies are found in the literature. Of these, ten are more or less complete descriptions. A study of these cases does not offer any solution as to the cause of the syndrome, but its association with cardiac disease is strongly emphasized. All the patients exhibited the typical symptom complex. Only the cardiovascular and important general anatomic findings are tabulated (table 1).

REPORT OF CASES

The following 2 cases are of special interest in that the patients in both died suddenly of dissecting aneurysm of the aorta.

CASE 1.—The patient, a 22 year old white university student, suddenly fell to the classroom floor and died on Jan. 15, 1935. He had been seen in the University of Chicago Clinics when he first entered the university in November 1933 and had had no complaints. He was described as an asthenic, 20 year old youth measuring 79 inches (200 cm.) in height and weighing 157 pounds (71 Kg.). The external occipital protuberance and the supraorbital ridges were prominent. The deeply set eyes showed bilateral iridodonesis and congenital subluxation of the lenses. The palate was high and arched. There was a sternal deformity of the pigeon breast type. The limbs, hands and feet were long and slender, and the gracile fingers and toes were remarkably long. Bilateral contractural deformities of the third, fourth and fifth toes were noted. The body musculature was poorly developed and hypotonic. All the joints were excessively mobile. The generalized lack of subcutaneous fat was distinct. The heart was of normal size. A loud systolic and a soft diastolic murmur were heard at the base, with greatest intensity in the aortic area. The pulse rate was 104, and the blood pressure was 130 systolic and 58 diastolic.

Past History.—The patient had been a normal full term infant at birth in September 1913. He had had bronchopneumonia at the age of 6. At the age of 9 an ophthalmologist had prescribed glasses after noting the presence of bilateral congenital subluxation of the lenses. A tonsillectomy had been performed the following year. There was no history of rheumatic fever or chorea.

His family physician later contributed more information. He had first seen the patient (aged 9) in 1922, having been consulted because of the child's nervousness. The aforementioned deformities and the presence of an apical systolic murmur were noted. He believed the child to be of a "pituitary type." In 1927 he observed twitchings in the muscles of the boy's forearms but no other significant changes. In 1934 the patient returned, complaining of headaches. He had grown 24 inches (61 cm.) in the intervening seven years. The possibility of a pituitary tumor was considered, and roentgenograms disclosed a definitely enlarged but

13. Passow, A.: Analogie und Koordination von Symptomen der Arachnodaktylie und des Status dysraphicus, Klin. Monatsbl. f. Augenh. **94**:102-103 (Jan.) 1935.

otherwise normal sella turcica. The blood pressure was 118 systolic and 62 diastolic. Loud systolic and soft diastolic basal murmurs were heard. An analgesic was prescribed for headache, and the patient was advised to limit his physical activity. The physician saw him for the last time in December 1934, one month prior to his death. He had been well and had no complaints. The blood pressure was 142 systolic and 80 diastolic. The pulse rate was 140 per minute. There were no other obvious changes in his physical condition.

Family History.—The patient's father and mother were living and well. Neither they nor their immediate relatives manifested any of the stigmas of arachnodactyly.

Autopsy.—The postmortem examination was performed twelve hours after death. The characteristic arachnodactylic abnormalities were as described in the clinical history. The main interest centered about the heart and aorta (fig. 1).

The pericardial sac was markedly distended and was found to be filled with 1,250 cc. of blood. There was a longitudinal tear in the intrapericardial portion of the ascending aorta. The pericardium, except for the area about the laceration,

Fig. 1.—Fusiform aortic aneurysm (case 1). The dilated sinuses of Valsalva are incorporated in the aneurysm, which terminates abruptly at the aortic arch. The tear lies high above the aortic valve. (Sections have been excised from its margin, and from the left cusp.)

was smooth and pale. The heart weighed 650 Gm. The right atrium and the tricuspid orifice were dilated. The right ventricle was small, and its muscular wall was firm and thick. The pulmonary orifice and the pulmonic trunk were normal. The ductus arteriosus and the foramen ovale were closed. The left atrium and the mitral orifice were normal. The muscle of the left ventricle was firm and hypertrophic. The aortic orifice measured 13 cm. The valve cusps were extremely large and thickened along the margins. The ostiums of the coronary arteries were located in an abnormally high position above the valve ring. The ascending aorta was dilated to approximately four times the normal size from the level of the valve ring upward for a distance of 14 cm. This dilatation formed a fusiform aneurysm measuring 19 cm. in its greatest circumference. The wall of the aneurysm was remarkably thin, striated and, in some areas, translucent. The dilatation ended abruptly 2 cm. below the innominate artery, and the aortic circumference was 5 cm.

at this point. The tear, 13 mm. long, was located 7 cm. above the junction of the right and posterior aortic valve cusps. It communicated with the pericardial cavity after dissecting downward for a distance of 3 cm.

The right pleural cavity was obliterated by dense fibrous adhesions. The lungs had red, wet sectioned surfaces. The liver was congested. The remaining organs were grossly normal.

Microscopic Examination: The most remarkable changes were found in the aortic media, and the lesions, although severest in the region of the aneurysmal dilatation, were found in all sections of the aorta (fig. 2). The changes consisted in rarefaction, fragmentation, and, in some areas, complete disappearance of the elastica associated with proliferation of muscle fibers. Instead of lying parallel to one another in the usual fashion, the fibers ran irregularly in all directions. Groups of muscle fibers surrounded spaces filled with a coagulum which stained blue with

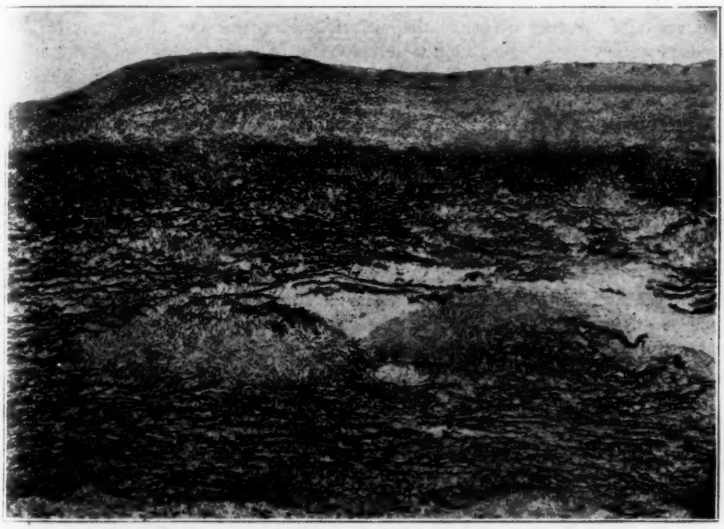

Fig. 2.—Aortic cystic medionecrosis (case 1). Muscle fibers are numerous in the aortic wall, and proliferation is conspicuous about the mucoid cysts and in spaces devoid of elastic lamellas. Phosphotungstic acid hematoxylin stain; × 55.

hematoxylin and eosin. The spaces varied from cleftlike slits to large cystic cavities. The intima was thickened over the larger cavities, and the adventitia was widened, containing small lymphocytic foci. A sudan III stain demonstrated no fatty deposits. There was no evidence in any section of medial inflammation or recent necrosis.

The hypertrophic myocardium exhibited focal scarring and small areas of cellular infiltration closely related to the intermuscular collagenous septums. The infiltrating cells were lymphocytes and eosinophils, with rare neutrophilic leukocytes. The leaflets of the aortic and mitral valves were thickened by a myxomatous fibrous tissue. Neither the valvular nor the myocardial lesions were typically rheumatic.

The liver also contained small numbers of lymphocytes, plasma cells and eosinophils about portal triads and central veins. The gastric mucosa was moderately atrophic and showed mild gastritis. The lungs, liver and pancreas were

congested. Sections of the anterior pituitary demonstrated poorly granulated basophilic cells and an apparent diffuse increase of small eosinophilic cells. The other endocrine glands and the thymus were normal. The testes contained few maturing spermatozoa.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: arachnodactyly; massive hemorrhage into the pericardial cavity secondary to rupture by dissection of a fusiform aneurysm of the ascending aorta; dilatation of the aortic orifice; malformation of the aortic media; cardiac hypertrophy; focal nonspecific myocarditis; scarring of the leaflets of the mitral and aortic valves; focal nonspecific hepatitis; subacute follicular and interstitial gastritis, and diffuse increase of eosinophilic cells in the hypophysis.

Case 2.—The patient, a 35 year old white woman, was first seen in the University Eye Clinic in 1931 at the age of 19. Her parents became aware of her visual disturbances when she was 6 years old. Her right eye had been enucleated at the age of 7 because of panophthalmitis following needling of a cataract. The ocular findings recorded in 1931 were coloboma of the left lens and choroid with tremulousness of the left iris. The patient was described as a thin woman appearing older than the stated age. The external occipital protuberance and the frontal eminences were prominent. The right orbital cavity contained an artificial eye. The palate was high and arched. There was severe thoracic deformity characterized by funnel chest and kyphoscoliosis of the dorsal spine. Other characteristic and noteworthy general findings were spider-like fingers and toes, long slender limbs, poorly developed hypotonic musculature, hypermobile joints and generalized lack of subcutaneous fat. There was no history of arachnodactyly in the family.

From 1935 to 1945 the patient was employed as recreational director of the Country Home for Crippled Children (University of Chicago). On two occasions during this period routine examinations demonstrated the presence of cardiac enlargement (70 per cent oversize) and a harsh basal systolic murmur. The blood pressure was 118 systolic and 66 diastolic. The only symptom, exertional dyspnea, was a minor one and never interfered with the patient's work or activities. She attended night school and completed most of the courses required for a bachelor's degree. In September 1945 she complained of scotoma in the left visual field. The retina became completely detached despite two attempts to refix it by microcoagulation, and within a short time total blindness ensued.

In the spring of 1946 she made plans to obtain a seeing-eye dog and was advised that she would be required to walk for an hour at a pace of three and one-half miles per hour. She began training to increase her tolerance to exercise. On the morning of May 4, 1946, she walked vigorously, returning home breathless. That afternoon at 4 p. m., while scrubbing the floor, she had sudden severe, constricting precordial pain without radiation and fainted. Unconsciousness persisted for five minutes. When revived, she became nauseated and vomited. Dyspnea appeared and became intense. She noted a tingling sensation in the fingers of her left hand. When admitted to Billings Hospital at 8 p. m. she was pale and extremely dyspneic. The pulse, though feeble, was regular at 66 per minute. The blood pressure was 100 systolic and 45 diastolic. A few crepitant rales were heard in the left pulmonary field. Inspection disclosed a heaving precordium, and percussion demonstrated massive cardiac enlargement. There was a harsh systolic thrill and murmur, of greatest intensity in the second and third left interspaces. The liver was barely palpable in a scaphoid abdomen. Intranasal administration of oxygen, sedation and complete rest in bed were ordered. The laboratory findings were as follows: hemoglobin content, 13 Gm.; red blood cells 4,720,000; white blood cells 14,050,

with 86 per cent neutrophils; sedimentation rate, 5 mm. per hour, and hematocrit reading, 44 per cent. A urinalysis yielded normal results. An electrocardiogram on May 6 showed a tendency to right axis deviation but no evidence of myocardial infarction. Precordial pain persisted, requiring relatively large quantities of morphine during the next five days. A second electrocardiogram, on May 9, demonstrated that notable changes had occurred since May 6. The previously upright T waves had become inverted or diphasic in all leads, and the isoelectric S-T intervals had become depressed in leads II and III. These changes were interpreted as the result of digitalization or of pericarditis rather than as indicative of myocardial infarction. On the morning of May 10 the patient was found to be pale, cold, perspiring and complaining of severe pain in the lower thoracic and upper lumbar regions of the back. Her respirations were labored. The blood pressure and pulse rate were not obtainable in the right arm but were readily detectable in the left. The blood pressure was 136 systolic and 56 diastolic. These changes were accompanied with a precipitous rise in pulse rate to 140 per minute, a rise in

Fig. 3.—Dissecting aneurysm of the aorta (case 2). The primary laceration lies above the aortic valve, and the false passage has been laid open from the arch to the diaphragm.

temperature to 103.5 F. and an increase in respirations to 44 to 56 per minute. The following day the liver was palpable at the umbilicus, and the white blood cell count was recorded as 44,000. All these signs and symptoms persisted, the pain being of particular severity and requiring "demerol" (1-methyl-4-phenyl piperidine 4-carbonic acid), until death on May 14.

Clinical Diagnosis.—The clinical diagnosis was as follows: arachnodactyly, congenital heart disease with intraventricular septal defect and coronary occlusion with myocardial infarction.

Autopsy.—The postmortem examination was performed three and one-half hours after death. The arachnodactylyic abnormalities were as described clinically. The heart and aorta were of greatest interest (fig. 3).

The pericardium was thin and translucent. In situ the entire right border of the heart was formed by the dilated right atrium. Because of the thoracic deformity the heart was twisted, and the pulmonary conus lay behind and to the left of the

aorta. The emptied heart weighed 590 Gm. The right atrium had a thick wall, and the auricle contained a small thrombus. The foramen ovale was closed. The dilated tricuspid orifice measured 14 cm., and the valve leaflets were thick and nodular. The distended and hypertrophied right ventricle had a firm wall 5 to 6 mm. thick. The pulmonary valve and the pulmonic trunk were normal. The endocardial surface of the dilated left atrium was gray-white and opaque, with a rough wrinkled area just above the anterior mitral leaflet (fig. 4). The mitral orifice was enlarged, measuring 13.5 cm. The leaflets and chordae tendineae were thick, gray-white and firm. The left ventricle was roomy but had a thick wall which measured 20 mm. near the base. The myocardium contained a large area of softening in the posterior-superior portion of the septum and the posterolateral wall of the left ventricle. The endocardial surface of the infarct was red-yellow, and the sectioned surfaces were hemorrhagic. The aortic orifice measured 8 cm., and its leaflets were fused and thick, with large nodules of Arantius. The left coronary artery was patent. A transverse tear, 2.5 cm. in length, was located 3.5 cm. above the aortic valve

Fig. 4.—Fibrous thickening of the mitral valve and left atrial endocardium (case 2).

(fig. 5). Blood forced through this intimal tear had dissected the media. The false passage included two thirds of the circumference of the aorta. It extended proximally to the aortic valve ring and peripherally to the iliac arteries. The dissection involved the wall of the right coronary artery. The inner medial layer of this artery was avulsed from a thin outer layer, and the space between was filled by a blood clot (fig. 6). The false passages in the innominate, superior mesenteric and right iliac arteries contained blood clots, while those in the left carotid and subclavian arteries contained fluid blood. The right renal and inferior mesenteric arteries were torn away from the inner wall and communicated only with the lumen of the dissecting aneurysm.

The right pleural cavity was twice the size of the left because of the severe kyphoscoliosis and the cardiac enlargement. The lower lobe of the left lung was compressed. The middle lobe of the right lung was rudimentary, consisting of a single lobule. Both lungs were congested and wet. The brain weighed 1,250 Gm. The

small size of the gray-white right optic nerve was the only gross abnormality. The body of the sacrum was a hollow shell filled by a thin-walled sac containing spinal fluid. Two fluid-filled sacs protruded through symmetric, 5 cm. size openings in the anterior sacral surface.

Microscopic Examination: The aortic medial changes were most outstanding in the region of the perforation but were easily detectable in all portions of both the thoracic and the abdominal aorta (fig. 7). The basic lesions were similar in all respects to those found in case 1. The plane of dissection in the aorta and its

Fig. 5.—Close view of the aortic laceration, which lies at the upper border of the dilated sinuses of Valsalva (case 2). Note the bulging wall about the right coronary ostium.

branches was close to the adventitia, and only a small portion of media remained with the outer layer. The myocardial fibers were hypertrophic, and small scars were seen in relation to collagenous septums. The infarct was obviously a fresh one, showing hemorrhage, incomplete necrosis of muscle fibers and little or no cellular infiltration. The leaflets of the tricuspid, mitral and aortic valves were thickened by myxomatous fibrous tissue. The mitral valve ring was calcified, and the adjacent myocardium contained dense hyaline scars. The endocardial surface

of the left atrium was thickened and thrown into verrucous folds composed of loose cellular connective tissue. These changes were not of the type seen as sequelae in rheumatic fever. The media of the pulmonary artery contained an excess of irregularly arranged muscle fibers.

There was an apparent preponderance of eosinophilic cells in the anterior pituitary. The thyroid was composed of small acini, half of which contained a normal amount of colloid. Groups of acini were separated by thick fibrous trabeculae infiltrated by lymphocytes. The other endocrine glands, the thymus and the generative organs were normal. Renal tubules contained many blue-staining (calcified) casts. The bone marrow was hyperplastic, with incomplete maturation of myeloid elements. There was passive congestion of the lungs, liver and spleen. The brain was normal.

Fig. 6.—Freshly clotted blood in the dissecting aneurysm, occluding the right coronary artery by tamponade (case 2). Hematoxylin and eosin stain; × 20.

Left Eye:[14] The eyeball was irregularly ovoid, measuring 25.5 mm. transversely, 26.5 mm. vertically and 28 mm. in the anteroposterior axis. The posterior segment appeared elongated and terminated in a small posterior staphyloma. The sclera was thin, and the retina was completely detached except at the ora serrata and the disk margin.

Histologic Examination: The conjunctiva and all layers of the cornea were normal. The canals of Schlemm were open, but only vestiges of Fontana's spaces were present in the rather compact meshwork of the iris angle. The iris was normal, but the ciliary muscle was attenuated, as is usual in high grade myopia. The much shrunken ciliary processes were directed posteriorly, and their epithelium had lost much of its pigment. The zonular fibrils supporting the lens were scanty and

14. The pathologic description was given by Dr. C. Keith Barnes

lax. Many of them showed an irregularly wavy or helical pattern. The lens capsule was thin, exceptionally so posteriorly. The lens substance was distorted by swelling and fragmentation of the subcapsular fibers posteriorly and by equatorial subcapsular clefts. Its inferonasal equatorial sector was rounded and drawn upward and toward the temple (in the region of the lens coloboma seen during life). The degenerated shrunken vitreous lay displaced forward and included scattered erythrocytes and a few pigment-bearing macrophages. The detached retina was edematous, and it was further distorted by adhesions between folds and by gliosis at the margin of an old tear. It overlay pools of protein-rich fluid. A tract of vascular reparative tissue extended from the ora serrata to a region on the temporal side of the macula. The choroid and sclera were thinned, especially posteriorly. The optic nerve head was moderately edematous. It had a connective tissue–covered meniscus and was

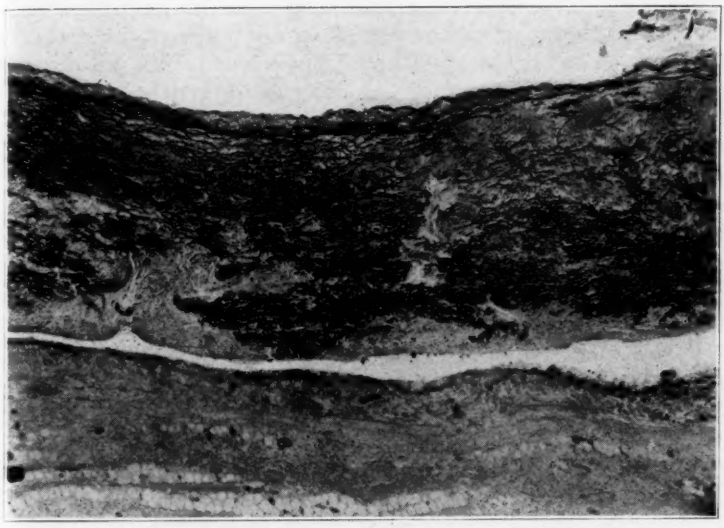

Fig. 7.—Aortic cystic medionecrosis and dissecting aneurysm (case 2). The dissection channel is close to the adventitial border. Weigert's stain for elastic fibers; × 55.

ringed by a zone of choroidal fibrosis. This zone contained few blood vessels, no pigment elements and no remnants of the glassy membrane.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: arachnodactyly; dissecting aneurysm of the aorta and its main branches; malformation of the aortic media; complete occlusion (due to tamponade by clotted blood in the false passage) of the right coronary artery and partial occlusion of the innominate, superior mesenteric and right iliac arteries; communication of the right renal and inferior mesenteric arteries with the dissecting aneurysm, secondary to avulsion of their ostiums from the inner wall of the false passage; acute myocardial infarction; cardiac hypertrophy; fibromyxomatous thickening of the tricuspid, mitral and aortic valves and of the left atrial endocardium; vestigial middle lobe of the right lung; atelectasis of the lower lobe of the left lung; atrophy of the thyroid; diffuse increase in

eosinophilic cells in the hypophysis; congenital anterior sacral meningocele; absence of the right eye, with atrophy of the right optic nerve; congenital and acquired defects of the left eye, and passive congestion of the lungs, liver and spleen.

COMMENT

Dissecting aneurysm of the aorta is reported in 2 adults with Marfan's syndrome. The first patient had been seen once prior to death. There were loud systolic and soft diastolic murmurs heard, with greatest intensity in the aortic area. A high pulse pressure was the only other clinical sign of aortic regurgitation recorded. The postmorten examination revealed cardiac hypertrophy, dilatation of the aortic orifice, displacement of the coronary ostiums upward and fusiform dilatation of the ascending aorta. Death resulted from perforation of this aneurysm by dissection into the pericardial sac. The second patient was observed at intervals for fifteen years. She had a harsh systolic murmur and thrill, of greatest intensity in the second and third left interspaces. She was believed to have congenital heart disease, with interventricular septal defect, but the cardiac signs were attributed in part to thoracic deformity. In her terminal illness the severe pain in the back and the absence of pulsation at the left wrist were important but disregarded clues to the diagnosis of dissecting aneurysm. The postmortem examination revealed an extensive dissecting aneurysm of the aorta. A unique finding was the extension of the dissection into the right coronary artery, with occlusion resulting from compression of the artery by a blood clot in the false passage. Death resulted from myocardial infarction rather than from rupture of the aneurysm. In both cases histologic examination of the aorta disclosed an identical malformation of the aortic media.

These 2 cases together with 4 previously reported [15] make a total of 6 in which there were aortic lesions in the fourteen necropsies performed on patients who had had arachnodactyly. These figures are highly significant if it is considered that 5 of the 8 patients with no described aortic lesions were under 28 months of age, while those with aortic lesions were between 14 and 35 years (table). The gross descriptions of the hearts and aortas are similar in the 6 cases. The lesions include cardiac hypertrophy, deformities of the aortic valve, dilatation of the aortic valve ring and varying degrees of dilatation of the sinuses of Valsalva and/or of the ascending portion of the aorta. Mural and valvular thickenings grossly resembling rheumatic lesions were seen in each case.

The endocardial changes in our cases proved not to be the rheumatic changes suspected grossly. The valves were thickened by myxomatous tissue similar to the gelatinous nodules often seen on the valves of the

15. Weill, G.: Ectopie des cristallins et malformations générales, Ann. d'ocul. **169**:21-44 (Jan.) 1932. Baer, Taussig and Openheimer.[5] Etter and Glover.[6]

hearts of normal infants and on the valves of hearts with congenital lesions. It seems probable that these endocardial lesions are manifestations of a developmental defect.

Changes in the aortic media resembling the lesions which we have described have been reported previously in 2 patients with arachnodactyly by Baer, Taussig and Oppenheimer.[5] These authors concluded that they were the result of a congenital abnormality. Detailed histologic descriptions of the aorta are lacking in the other 10 case reports. The conclusion that the aortic medial lesions in Marfan's syndrome are the result of a congenital defect seems reasonable, but it must be admitted that these lesions are indistinguishable from "medionecrosis aortae idiopathica cystica" described by Erdheim.[16] This author and Rottino[17] have stressed the peculiarities of this type of aortic medionecrosis, particularly the abundance and abnormal arrangement of smooth muscle fibers, which they attributed to reparative hyperplasia. The derangement of the smooth muscle fibers, the rarefaction, fragmentation and distorted pattern of elastic lamellas and the presence of mucoid-filled cystic spaces are distinctive characteristics of this aortic medial lesion. In most instances it has been reported (Erdheim and others) in middle-aged and elderly persons with a history of hypertension. It seems incredible that the similar lesions found at necropsy in such a high proportion of nonhypertensive adolescents and young adults with arachnodactyly are of identical origin. However, it is not possible at this time to confirm or deny that the aortic medionecrosis in Marfan's syndrome is of a developmental nature, nor can the true incidence and importance of the aortic lesions be evaluated from existing data on necropsies. The aortas of all persons with Marfan's syndrome should be examined carefully whether or not they exhibit unusual gross changes. The possibility of formes frustes of Marfan's syndrome should be considered whenever dissecting aneurysm or unexplained widening of the ascending aorta is suspected clinically or found at autopsy.

The possible role of the endocrine glands in Marfan's syndrome has been debated repeatedly. There is no anatomic evidence to implicate any of them but the hypophysis. In cases 1 and 2 the hypophysis appeared to contain more than the usual proportion of eosinophilic cells. Weill[15] made the same observation in an adult, and Salle,[12] Börger[18] and Bergstrand[19] found a similar change in infants. No increase of

16. Erdheim, J.: Medionecrosis aortae idiopathica cystica, Virchows Arch. f. path. Anat. **276**:187-229, 1930.

17. Rottino, A.: Medial Degeneration of the Aorta as Seen in Twelve Cases of Dissecting Aneurysm, Arch. Path. **28**:1-10 (July) 1939.

18. Börger, F.: Ueber zwei Fälle von Arachnodaktylie, Ztschr. f. Kinderh. **12**:161-184, 1915.

19. Bergstrand, C. G.: Beitrag zur pathologischen Anatomie der Arachnodaktylie, mit Bericht über einen eigenen Fall, Acta pædiat. **30**:345-363, 1943.

eosinophilic cells was found in 5 other cases. Hormonal studies have been few, and none of the existing evidence clarifies the role of the hypophysis.

SUMMARY

The clinical characteristics of Marfan's syndrome are discussed, particularly as manifested in adults. The significant lesions observed in twelve autopsies, seven of which were performed on adolescents or adults, are tabulated. Cardiovascular lesions are common and especially important. They include aortic medial necrosis and endocardial lesions which simulate those of rheumatic fever. The former is the more dangerous, resulting in dilatation of the aortic valve ring, the sinuses of Valsalva and the ascending portion of the aorta. Death may occur suddenly from dissecting aneurysm and rupture of the aorta. The role of the endocrine glands, particularly the hypophysis, remains obscure. Clinical data and complete data on the necropsies are presented for 2 adults with arachnodactyly, both of whom died as the result of dissecting aneurysm of the aorta.

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EFFECTS ON THE CARDIOVASCULAR SYSTEM OF FLUIDS ADMINISTERED INTRAVENOUSLY IN MAN

V. Function of Cutaneous Capillaries and Lymphatic Vessels

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AND

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EARLIER studies from this and other laboratories[1] have yielded data on the nature of the changes in the dynamics of the circulation in patients receiving infusions of electrolytes intravenously. All authors agree that such infusions increase blood volume, raise venous and intra-auricular pressures and increase cardiac output; changes in arterial pressure are variable. There are, however, no data available

From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

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on changes in the function of small vessels during the course of intravenous infusions in man, and it was therefore considered of interest to make the present study.

MATERIAL AND METHODS

Seven men, 16 to 58 years old, were studied; none had any evidence of cardiovascular disease. Each received an infusion into an antecubital vein of 1,800 cc. of isotonic solution of sodium chloride or 5 per cent dextrose in isotonic solution of sodium chloride; the rates of infusion were between 60 and 85 cc. per minute (table).

The venous pressure was measured by means of the method of Moritz and von Tabora,[2] and lymphatic function was studied by means of a method suggested by Griffith and others[3]; after cleansing of the skin with xylene, the capillaries of the finger nail fold were observed under oil by means of a microscope with a magnification of 100 or 200 times.

OBSERVATIONS

Capillary Flow.—Before the beginning of the infusion, the capillaries of the finger nail fold were normal in appearance in every patient; they were visible in only small numbers, and flow in them was slow. No change was observed until several hundred cubic centimeters of fluid had been given intravenously. Thereafter, additional capillary loops became visible. All visible vessels were wider than normal, and blood flow was greatly accelerated; in some instances the capillaries were seen to pulsate markedly. These changes were progressive and became maximal usually before, but occasionally after, the end of the period of infusion of fluid, i.e., when 1,000 to 1,800 cc. had been given. Thereafter, the findings remained unchanged until the intravenous infusion was ended. Within a few minutes after the termination of the infusion the degree of change from the normal in the capillaries became less, and over a period of twenty to forty minutes most or all of the change disappeared.

Lymphatic Function.—Wheals containing dye showed no increase or only small increases in size in fifteen to twenty minute periods be-

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IX. The Treatment of Shock with Concentrated Human Serum Albumin; Preliminary Report, ibid. **23**:506, 1944. (*i*) Fletcher, A. G.; Hardy, J. D.; Riegel, C., and Koop, C. E.: Gelatin as a Plasma Substitute: The Effect of Intravenous Infusion of Gelatin on Cardiac Output and Other Aspects of the Circulation of Normal Persons, of Chronically Ill Patients, and of Normal Volunteers Subjected to Large Hemorrhage, ibid. **25**:405, 1944.

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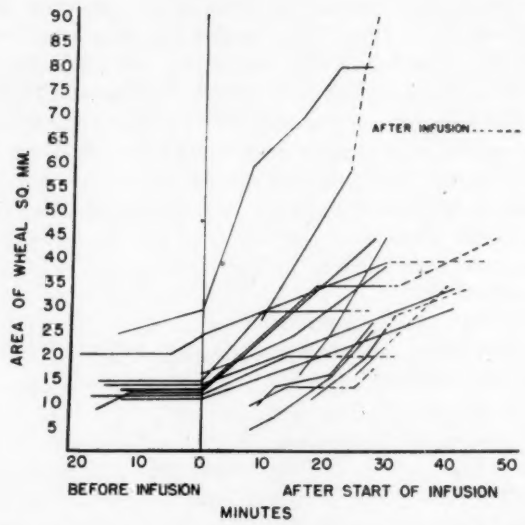

Increase in size of cutaneous wheals during intravenous infusions.

Results of Intravenous Infusion of Fluids in Eight Patients

Case	Solution Infused	Average Rate of Infusion, Cc./Min.	Venous Pressure, Cm. of Water: Before Infusion	Venous Pressure, Cm. of Water: At End of Infusion	Percentage Increase in Area of Wheal: Before Infusion	Percentage Increase in Area of Wheal: During Infusion	Site of Wheal
G	5% dextrose in isotonic solution of sodium chloride	60	2.4	13.6	1) 52	250	Same arm as infusion
					2) —	50	Same arm as infusion
					3)	178	Same arm as infusion
A	5% dextrose in isotonic solution of sodium chloride	60	7.4	11.8	1) 0	172	Arm opposite to infusion
					2) —	115	Arm opposite to infusion
E	5% dextrose in isotonic solution of sodium chloride	80	9.7	15.7	1) 0	98	Same arm as infusion
					2) —	556	Same arm as infusion
P	Isotonic solution of sodium chloride	60	5.6	12.7	1) 21	62	Thigh
					2) —	145	Thigh
W	Isotonic solution of sodium chloride	85	7.3	14.6	1) 0	56	Shoulder of same arm as infusion
					2) —	92	Shoulder of same arm as infusion
T	Isotonic solution of sodium chloride	60	8.4	17.0	1) 15	157	Same arm as infusion
					2) 15	202	Arm opposite to infusion
					3) —	66	Same arm as infusion
					4) —	225	Arm opposite to infusion
C	Isotonic solution of sodium chloride	75	1.0	6.7	19	137	Same arm as infusion

fore the start of the infusion; the increases in area ranged from 0 to 52 per cent and averaged 15 per cent (table and figure). During the infusion, wheals previously made and newly made wheals increased in area by 50 to 556 per cent; the average increase was 160 per cent (table and figure). The location of the wheals did not appear to influence the degree of increase. In most instances streamers radiating out from the wheals appeared during the infusions of fluid intravenously; these ranged in length up to 6 mm. No correlation was found between the increase in size of the wheals in the skin and the rise in venous pressure induced by the infusion (table).

COMMENT

More than seventy years ago von Lesser,[4] after studies of the effects of transfusions on dogs, concluded that "the excess of blood accumulates principally in the small vessels." The conclusion that the final adjustment of the circulation to an intravenous infusion was a progressive dilatation of small blood vessels was subsequently restated by Meek and Eyster[5] and Altschule and Gilligan.[1b] The present work supports these earlier conclusions and in addition corroborates the direct observations of Meek and Eyster on the capillaries of the omentum of dogs receiving infusions.

The enormous distensibility of the finest portions of the vascular bed is well known. When, however, the vascular bed is overdistended, as in patients with chronic congestive failure, severe pulmonary disease or polycythemia vera, compensation for increases in blood volume consequent to intravenous infusions is impaired; the venous pressure rises abnormally, and untoward symptoms may occur.[6]

The present observations, which indicate an increase in lymphatic flow during intravenous infusions of solutions of electrolytes, are in harmony with the concept that such fluids leave the circulation rapidly and that only a portion of the volume given can be found in the circulation at the end of the period of infusion.[1a] The loss of fluid from the circulation is probably the consequence of an increased filtering pressure and also of expansion of the filtering bed. On the other hand, the increase in activity of the lymphatic vessels indicates that some of the extravasated fluid is returned to the circulation. This last conclu-

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5. Meek, W. J., and Eyster, J. A. E.: The Effect of Plethora and Variations in Venous Blood Pressure on Diastolic Size and Output of the Heart, Am. J. Physiol. **61**:186, 1922.

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sion is of interest in relation to possible differences in the effects of infusions on patients with cardiac edema and on those with nephritic edema. In the latter lymphatic function is greatly accelerated,[7] and it is probable therefore that extravasated fluid reenters the circulation readily; a strong tendency toward the development of pulmonary edema exists in such patients. In patients with cardiac edema, on the other hand, lymphatic function is impaired,[7] and presumably extravasated fluid tends to remain in the tissues; many patients with cardiac disease tolerate infusions of isotonic solutions of sodium chloride remarkably well.[6]

The fact that evidence of loss of fluid from the circulation exists in patients receiving infusions of solutions of electrolytes is also of clinical interest. The two tissues of greatest water content are the skin and the pulmonary parenchyma. Accumulation of fluid consequent to increased filtration from the circulation is presumably greatest in these two tissues. Large volumes of fluid may exist in the skin without causing symptoms and without being detectable by clinical examination. In the case of the lungs, however, the accumulation of excessive fluid may precipitate respiratory signs and symptoms. Accordingly, it is not surprising that in patients in whom pulmonary edema is latent because of the presence of cardiac or pulmonary disease, uremia, disorders of the central nervous system or other conditions overt manifestations of that disorder may be caused during or after the intravenous infusions of a solution of electrolytes.

SUMMARY AND CONCLUSIONS

Capillary microscopy reveals a progressive dilatation of the small blood vessels of the finger nail fold during intravenous infusions; blood flow is greatly accelerated. Cutaneous lymphatic flow is greatly increased during intravenous infusions of solutions of electrolytes, apparently as a consequence of the loss of fluid from the circulation.

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SENSITIVITY OF SKIN TO HISTOPLASMIN IN DIFFERENTIAL DIAGNOSIS OF PULMONARY DISEASE

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DURING the period of rapid demobilization of the United States Army following cessation of hostilities, many soldiers were found to have roentgenologic evidence of pulmonary pathema. This was discovered at routine physical examination during the process of their separation from the Service. More than 1,500 patients were sent to the Moore General Hospital from various separation centers over the country because of roentgenologic evidence of pulmonary disease. Most of them were asymptomatic. Their sputum on repeated examinations was negative for acid-fast organisms in more than 50 per cent of the cases. Of the total number, 3.5 per cent had a negative reaction to the cutaneous test for tuberculin. For the most part, these patients were to be observed for a period of at least six months. This period of observation was necessary to determine the presence of activity. All patients were considered to have pulmonary tuberculosis until it was proved otherwise. The disease was considered to be active until the men were observed for six months, after which the men were classified, and when their condition was arrested they were discharged from the Service in compliance with existing directives.

It is apparent that this was a difficult diagnostic problem. Some of the patients were proved to have coccidioidomycosis on examination of the sputum and by positive reactions to the complement fixation test and the precipitin tests. In others the condition was never given a

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definite diagnosis but was presumptively diagnosed as pulmonary tuberculosis, inactive or arrested.

Palmer's report [1] on nontuberculous pulmonary calcification and sensitivity to histoplasmin and the epidemiologic study of pulmonary lesions in Ohio by Olsen, Wright and Nolan [2] indicated that a study of the sensitivity of the skin to histoplasmin in these patients might offer a solution to the problem. Christie [3] has already shown that pulmonary calcifications do exist in certain young persons who apparently have not had tuberculosis. These persons frequently exhibit sensitivity of the skin to histoplasmin.

It is well known that many of the fungus infections show a cross sensitivity reaction. Injections of histoplasmin, coccidioidin, haplosporangin and blastomycin produce cross reactions that have been clearly demonstrated in animals.[4]

METHOD OF STUDY

The cutaneous tests were done in a battery of three, with a control of the diluting fluid. The following antigens were given: (1) tuberculin—0.00002 mg. of purified protein derivative in 0.1 cc. of fluid, (2) coccidioidin (C. E. Smith)—1 to 1,000 dilution in 0.1 cc. of fluid and (3) histoplasmin (Army Institute of Pathology)—1 to 1,000 dilution in 0.1 cc. of fluid. All tests were made on the left arm at the same time by one technician. The same technician read the results by measuring the area of induration and erythema. Any area of less than 5 by 5 mm. was considered to indicate a negative reaction, and the second strength solutions were used as follows: (1) tuberculin—0.005 mg. of purified protein derivative in 0.1 cc. of fluid, (2) coccidioidin—1 to 10 dilution in 0.1 cc. of fluid and (3) histoplasmin—1 to 10 dilution in 0.1 cc. of fluid. All tests were given intradermally in the manner prescribed for administration of the tuberculin test.

Cultures were planted in duplicate sets. One set remained at room temperature, and the other was incubated at 37 C. Both sets were held for six weeks before being reported as sterile. Each set consisted of: (1) beef infusion broth tubes, (2) Sabouraud's agar slants, (3) corn meal agar slants and (4) blood agar slants. The technic was good. Only two contaminants occurred in over one hundred and twenty sets.

To correlate epidemiologic, clinical, roentgenologic and laboratory data, a form was prepared indicating the state of birth, countries and states visited, roentgenologic characteristics of pulmonary lesions, physical condition and the history

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4. Emmons, C. W.; Olsen, B. J., and Eldridge, W. W.: Studies of the Role of Fungi in Pulmonary Disease, Pub. Health Rep. **60**:1383-1394, 1945. Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**:790-807, 1943.

of previous pulmonary diseases. In addition, on all patients showing strongly positive reactions to histoplasmin biopsies of lymph nodes and aspirations of sternal marrow were carried out for culture and histologic examination.

RESULTS OF THE STUDY

A total of 1,220 persons were tested. Table 1 shows the distribution of tests with respect to the degree of sensitivity and the combinations

TABLE 1.—*Sensitivity of the Skin by Sensitivity Groups Showing Degree of Reaction by Area of Induration*

		Area of Induration								No. of Persons
		5-10 Mm.	10-20 Mm.	20-30 Mm.	30-40 Mm.	40-50 Mm.	50-60 Mm.	60-70 Mm.	Total	
Group 1		...	...	..	..	..	..	..	...	293
Tuberculin	1st	86	133	34	14	2	..	1	270	
	2d	4	7	4	7	1	..	..	23	
Coccidioidin	1st	136	20	5	2	..	..	..	163	
	2d	94	28	4	2	2	..	..	130	
Histoplasmin	1st	123	46	2	1	1	..	..	173	
	2d	60	48	8	2	1	..	1	120	
Group 2		...	...	..	..	..	..	..	...	75
Tuberculin	1st	29	19	5	2	..	..	..	55	
	2d	3	10	3	2	2	..	..	20	
Coccidioidin	1st	23	8	..	..	..	..	..	31	
	2d	29	12	2	1	..	..	..	44	
Group 3		...	...	..	..	..	..	..	...	397
Tuberculin	1st	138	114	33	6	1	..	..	292	
	2d	14	55	26	8	1	1	..	105	
Histoplasmin	1st	140	23	3	1	..	..	..	167	
	2d	110	91	21	3	5	..	..	230	
Group 4		...	...	..	..	..	..	..	...	4
Coccidioidin	1st	1	...	..	..	..	..	..	1	
	2d	2	1	..	..	..	..	..	3	
Histoplasmin	1st	1	...	..	..	..	..	..	1	
	2d	2	1	..	..	..	..	..	3	
Group 5		...	...	..	..	..	..	..	...	413
Tuberculin	1st	86	118	16	5	..	..	..	225	
	2d	25	77	60	20	2	1	3	188	
Group 6		...	...	..	..	..	..	..	...	7
Coccidioidin	1st	...	...	..	..	..	..	..	...	
	2d	2	2	2	..	..	..	1	7	
Group 7		...	...	..	..	..	..	..	...	21
Histoplasmin	1st	2	2	..	..	..	..	..	4	
	2d	6	8	2	..	..	..	..	17	
Total number of persons										1,220

of sensitivity which occurred. It is apparent from this table that by far the largest number showed only a mild reaction to histoplasmin, the area being under 15 mm. in diameter. The patients were grouped according to sensitivity to each of the three antigens. This grouping is shown by the bar diagrams in figure 1, *A* showing the percentage of patients sensitive to tuberculin by sensitivity groups. The open bars show the accumulative percentage of sensitivity to tuberculin as influenced by adding patients with sensitivity combinations as indicated in

the diagram. Parts *B* and *C* give similar information for sensitivity to histoplasmin and coccidioidin.

It has been noted that in practically every instance in which a strongly positive reaction (20 mm. and over) was obtained to histoplasmin in the first strength, a weakly positive reaction (5 to 10 mm.) was obtained to coccidioidin in the second strength. Similarly, a strong positive reaction (20 mm. and over) to coccidioidin in the first strength was usually accompanied with a mild reaction to histoplasmin in the second strength (5 to 10 mm.).

Of the 1,220 patients studied, only 528 were followed for a sufficient length of time to complete the clinical observations. Of the 528, 117

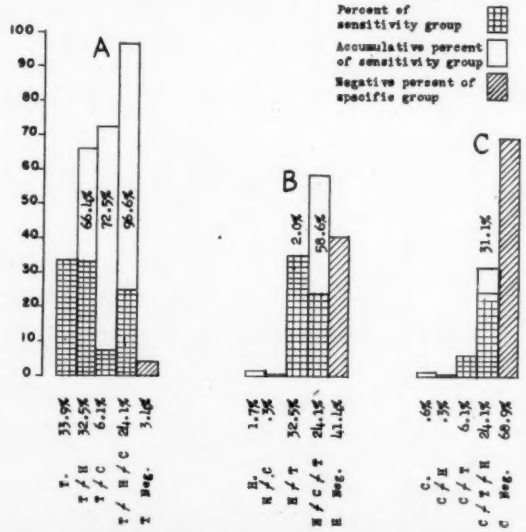

Fig. 1.—Bar diagram showing relative frequency of sensitivity of the skin to tuberculin (*T*), coccidioidin (*C*) and histoplasmin (*H*). Cross-hatched bars indicate the specific combinations in which sensitivity occurred. The open bars show the accumulative specific sensitivity to each antigen as influenced by adding various sensitivity groups as indicated at the base of each bar.

were ultimately found to have acid-fast bacilli in their sputum. The few patients with anemia responded well to iron and vitamin therapy. The hemoglobin content, the white blood cell count and the temperature varied so greatly that a statistical study of these factors was considered to be of no value.

The factors considered to be of most importance in the study are given in table 2. Here, certain roentgenologic findings together with the physical symptoms and a history of pain in the chest and of previous attacks of pleurisy are recorded for the three sensitivity groups. The

TABLE 2.—*Clinical and Roentgenologic Observations Among Five Hundred and Twenty-Eight Patients with Respect to Sensitivity to Tuberculin, Histoplasmin and Coccidioidin*

Clinical Factors Occurring in 528 Patients		Sensitivity to Tuberculin (491, or 93%)				Sensitivity to Histoplasmin (256, or 48%)				Sensitivity to Coccidioidin (161, or 30%)			
		No. of Patients	Percentage of Total Factors	Expected Occurrence	Column 3 Minus Column 4	No. of Patients	Percentage of Total Factors	Expected Occurrence	Column 7 Minus Column 8	No. of Patients	Percentage of Total Factors	Expected Occurrence	Column 11 Minus Column 12
	1	2	3	4	5	6	7	8	9	10	11	12	13
Roentgenologic lesion, diffuse	339	310	91.5	93.0	—1.5	169	49.7	48.0	+1.7	93	27.4	30.0	—2.6
Roentgenologic lesion, discrete	186	171	92.0	93.0	—1.0	90	47.4	48.0	—0.6	58	31.1	30.0	+1.1
Hilar calcifications	60	54	90.0	93.0	—3.0	36	60.0	48.0	+12.0	21	35.0	30.0	+5.0
Parenchymal calcifications	107	96	98.7	93.0	+5.7	76	62.6	48.0	+14.6	38	35.5	30.0	+5.5
Fibrotic lesion	419	380	90.7	93.0	—2.3	202	47.2	48.0	—0.8	125	29.9	30.0	—0.1
Exudative lesion	344	323	93.7	93.0	+0.7	180	52.3	48.0	+14.3	115	33.4	30.0	+3.4
Cavitation	164	152	92.8	93.0	—0.2	79	48.1	48.0	—0.1	46	28.0	30.0	—2.0
Pain in upper part of the chest	62	50	80.7	93.0	—12.3	29	46.8	48.0	—1.2	22	35.4	30.0	+5.4
Pain in lower part of the chest	44	31	70.5	93.0	—22.5	21	42.7	48.0	—5.3	9	20.4	30.0	—9.6
History of pleuritis	61	59	96.7	93.0	+3.7	14	23.0	48.0	—25.0	9	16.4	30.0	—13.6
Pleural thickening	110	101	92.0	93.0	—1.0	53	48.3	48.0	+0.3	26	23.6	30.0	—6.4
Splenomegaly	17	16	94.2	93.0	+1.2	7	41.2	48.0	—6.8	4	23.5	30.0	—6.5
Hepatomegaly	11	9	81.7	93.0	—11.3	4	36.3	48.0	—11.7	3	27.3	30.0	—2.7
Lymphadenopathy	341	301	88.2	93.0	—4.8	165	48.5	48.0	+0.5	98	28.7	30.0	—1.3

total number of clinical factors are tabulated, and the number occurring in each sensitivity group is recorded as a percentage of the total number for each factor in the entire group. The expected number of factors, if not influenced by sensitivity of the skin, should parallel roughly the percentage for each sensitivity group, which is 93 per cent for tuberculin, 48 per cent for histoplasmin and 30 per cent for coccidioidin as related to the whole number of 528. By subtraction of the observed percentage of factors from the expected percentage, the difference is obtained for each factor in each sensitivity group.

While there was a statistically significant difference between the occurrence of pulmonary calcifications in the group with sensitivity to histoplasmin, it must be remembered that many of the patients were

TABLE 3.—*Anatomic Location of Pulmonary Calcifications with Respect to Sensitivity to Tuberculin, Histoplasmin and Coccidioidin*

Antigen	Total No. of Patients with Calcifications	Patients with Pulmonary Calcifications, %	Multiple Hilar Calcifications	Single Hilar Calcifications	Patients with Hilar Calcifications, %	Multiple Parenchymal Calcifications	Single Parenchymal Calcifications	Patients with Parenchymal Calcifications, %
Tuberculin only (209)....	44	15.3	12	4	5.52	22	6	13.4
Tuberculin and coccidioidin (38).....	12	31.6	3	1	10.5	5	3	21.0
Tuberculin and histoplasmin (127).....	50	39.3	16	1	13.4	21	12	26.0
Tuberculin, coccidioidin and histoplasmin (117)	44	34.6	10	7	14.5	15	12	23.0
Coccidioidin only (4)....	1	25.0	0	0	0.0	1	0	25.0
Histoplasmin only (10)..	7	70.0	2	0	20.0	3	2	50.0
Coccidioidin and histoplasmin (2).....	2	100.0	0	0	0.0	1	1	100.0
All tests negative (21)...	7	33.3	3	1	19.3	2	1	14.3
Total.....	167		46	14		70	37	

also sensitive to tuberculin and coccidioidin, as shown in the bar diagram in figure 1. For this reason it is difficult to make a definite statement. However, it is evident that the group of patients with sensitivity of the skin to histoplasmin showed a higher percentage of pulmonary calcifications than a similar group of patients with sensitivity of the skin to tuberculin. That is to say, the percentage of the 528 patients with sensitivity to histoplasmin (48 per cent) included 62 per cent of the patients with pulmonary calcifications in the parenchyma and 60 per cent of the patients with hilar calcification. Of the 528, 93 per cent were sensitive to tuberculin, and this number included 90 per cent of the patients with hilar calcification and 98 per cent of the patients with parenchymal calcifications. Of 10 patients who were sensitive to histoplasmin and not to tuberculin and coccidioidin, 7, or 70 per cent, had pulmonary calcifications. Table 3 shows the distribution of 167 patients with pulmonary calcifications.

The 528 patients were studied to determine geographic influence on the incidence of sensitivity to histoplasmin. Recent studies [3] would lead to the belief that Tennessee, Virginia, Kentucky, Ohio and Penn-

TABLE 4.—*Tabulation by States of Patients With and Without Sensitivity of the Skin to Histoplasmin and in Relation to Its Combinations with Tuberculin and Coccidioidin*

State	Histoplasmin Only	Histoplasmin and Coccidioidin	Histoplasmin and Tuberculin	Histoplasmin, Coccidioidin and Tuberculin	Total Number with Positive Reactions to Histoplasmin	Number with Negative Reactions to Histoplasmin	State Total	Percentage of Total Number with Positive Reactions to Histoplasmin
Alabama	..	..	4	5	9	7	16	56
Arkansas	..	..	4	2	6	..	6	100
Arizona	..	..	..	1	1	..	1	100
Connecticut	..	..	1	2	3	2	5	60
California	..	..	4	2	6	5	11	55
Colorado	..	..	1	..	1	..	1	100
Delaware	..	..	1	..	1	1	2	50
Florida	..	..	1	..	1	4	5	20
Georgia	..	..	3	5	8	5	13	62
Iowa	..	..	2	1	3	3	6	50
Idaho	..	..	..	..	..	..	..	..
Illinois	..	..	12	9	21	10	31	68
Indiana	..	..	8	3	11	3	14	79
Kentucky	1	..	6	8	15	12	27	56
Kansas	..	..	1	..	1	4	5	20
Louisiana	..	..	5	..	5	2	7	71
Mississippi	..	..	1	1	2	5	7	29
Missouri	..	..	4	1	5	5	10	50
Massachusetts	1	..	4	1	6	13	19	32
Michigan	..	..	2	4	6	8	14	43
Maine	..	..	1	..	1	1	2	50
Maryland	1	..	2	2	5	3	8	63
Minnesota	..	..	..	4	4	10	14	29
Montana	..	..	..	1	1	..	1	100
New Jersey	1	..	2	..	3	9	12	25
New York	1	1	13	11	26	35	61	43
New Mexico	..	..	..	..	..	..	..	..
North Dakota	..	..	..	..	..	..	..	..
North Carolina	1	..	4	3	8	14	22	36
Nebraska	..	..	..	..	..	1	1	..
New Hampshire	..	..	..	..	..	1	1	..
Nevada	..	..	..	..	..	..	..	..
Oregon	..	..	..	..	..	2	2	..
Ohio	..	..	10	1	11	9	20	55
Oklahoma	..	..	2	2	4	5	9	44
Pennsylvania	2	..	14	11	27	29	56	48
Rhode Island	..	..	..	..	..	2	2	..
South Carolina	..	..	1	1	2	7	9	22
South Dakota	..	..	..	..	..	..	..	..
Tennessee	2	..	10	8	20	13	33	61
Texas	..	..	2	4	6	9	15	40
Utah	..	..	..	..	..	..	..	..
Vermont	..	..	..	..	..	1	1	..
Virginia	..	..	3	6	9	13	22	41
Washington	..	..	..	2	2	5	7	29
West Virginia	..	..	5	2	7	9	16	44
Wisconsin	1	1	4	1	7	9	16	44
Wyoming	..	..	..	1	1	..	1	100
Washington, D. C.	..	..	3	2	5	1	6	83
Honolulu	..	..	..	1	1	..	1	100
Canada	..	..	..	..	..	1	..	..

sylvania have the highest percentage of persons with positive reactions. However, table 4 shows that this is not necessarily true. The numbers are too small for the West and Middle West to draw any definite conclusion, but the spot map (fig. 2) indicates the location by state of

the entire 528 patients, both those with negative and those with positive reactions. The points on this map indicate the state in which the patient had lived longest and considered to be his home. It does not necessarily indicate the state of birth or the location of his present home. An effort was made to correlate sensitivity of the skin with the states and foreign countries visited by the patients. This proved to be a hopeless task, as more than 90 per cent of the 528 patients had been in several of the states known to exhibit a high percentage of persons sensitive to histoplasmin.

Sensitivity to histoplasmin has been associated with pulmonary calcifications and, in the fatal cases of histoplasmosis, with involvement of the reticuloendothelial system and enlargement of the spleen, liver

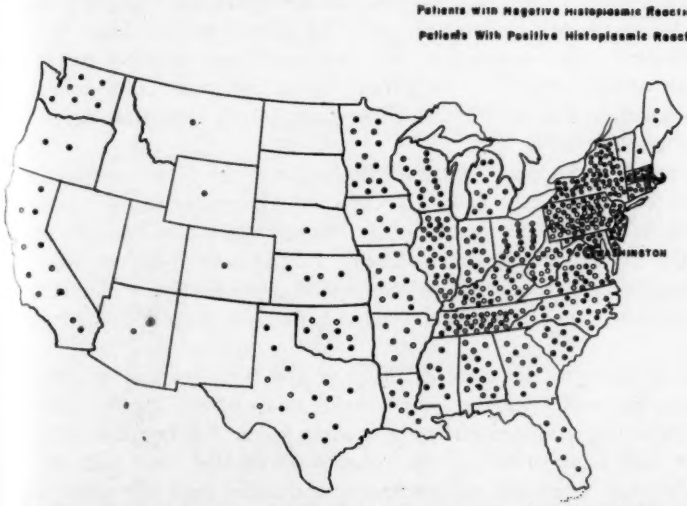

Fig. 2.—Spot map of the United States, showing distribution of 528 cases of pulmonary involvement with respect to sensitivity of the skin to histoplasmin.

and lymph nodes. Christie [3] reported the case of a soldier discharged from the Army because of many pulmonary calcifications, with a negative reaction to the tuberculin test and a complete lack of symptoms accompanying a strong sensitivity of the skin to histoplasmin. The calcifications apparently developed during the two year period the soldier was in the Service. In the same article Christie reported the case of a 10 month old boy who died from the results of a bilateral subdural hematoma. Autopsy showed enlarged tracheobronchial lymph nodes, with lesions of multinucleated giant cells lying among large mononuclear cells, surrounded by a zone of endothelial cells. The lesions did not show calcifications or caseations. The hilar nodes showed hyperplasia. The

liver and spleen had small granulomatous lesions of a similar character. Histoplasma capsulatum was isolated from the hilar lymph nodes, but Christie was of the opinion that the child did not die of the infection caused by this organism. The infant also exhibited two discrete lesions in the lower lobes of the lungs, which did show evidence of calcification.

The possibility of subclinical infection with H. capsulatum having been assumed for our patients with a strong sensitivity of the skin to histoplasmin (more than 20 mm.), an effort was made to isolate the organism. During the months of June, July and August, 81 patients were selected for special study. These patients all had a sensitivity of the skin indicated by an area of induration and erythema of more than 20 mm. in diameter. Table 5 shows the composition of this group with respect to sensitivity to tuberculin, coccidioidin and histoplasmin. Column 1 indicates the number of patients showing the clinical factors listed in the left margin. Forty persons, or 49.4 per cent, were sensitive to histoplasmin and tuberculin. Thirty-four, or 42 per cent, were sensitive to histoplasmin and coccidioidin. Seven, or 8.6 per cent, were sensitive to histoplasmin only.

A careful search for characteristic bodies in the large mononuclear cells of the bone marrow failed to reveal any H. capsulatum. If present in a viable form in this material, the fungus would have been detected with the methods of culture employed. It is possible, however, that an occasional organism would have been missed on microscopic examination. In no instance was H. capsulatum isolated from any of the patients in this series.

In addition to the cultures made of the bone marrow of the 81 patients, material from the lymph nodes was cultured for 11 patients showing a progressive exudative pulmonary lesion with negative reaction of the skin to tuberculin. The nodes were divided; one half of the material was fixed for microscopic examination, and the other half was crushed and cultured exactly as was done with the sternal marrow. Again all cultures were sterile, and the microscopic examination revealed only hyperplasia of the lymph nodes. All 11 patients revealed a strongly positive reaction to histoplasmin and a negative reaction to tuberculin in doses of 0.1 mg. of purified protein derivative. However, during the course of six months a sensitivity to tuberculin in the same doses did develop in 4 of the patients. The remaining 7 continued to have a negative reaction even to injections of 0.1 mg. The lesions in the 11 patients were similar in these respects: (1) they were all of the upper lobe; (2) they were exudative; (3) they progressed for two to three months; (4) they regressed for one to two months, and (5) they remained stable for six months.

After six months' observation with no evidence of tuberculous activity, the men were discharged from the hospital. The 4 patients in whom

TABLE 5.—*Clinical and Roentgenologic Observations on Eighty-One Patients with a Strong Reaction (20 mm. and over) to Histoplasmin Alone and in Combination with Tuberculin and Coccidioidin*

Clinical Factors Occurring in 81 Patients with a Strong Reaction to Histoplasmin	Number of Patients	Sensitive to Histoplasmin (81 Persons, or 100%)			Sensitive to Histoplasmin and Tuberculin (40 Persons, or 49.4%)			Sensitive to Histoplasmin and Coccidioidin (34 Persons, or 42%)			Sensitive to Histoplasmin Only (7 Persons, or 8.6%)		
		Occurrence, %	Expected Occurrence, %	Difference	Occurrence, %	Expected Occurrence, %	Difference	Occurrence, %	Expected Occurrence, %	Difference	Occurrence, %	Expected Occurrence, %	Difference
	1	2	3	4	5	6	7	8	9	10	11	12	13
Pulmonary calcifications	36	100	100	0	89	49.4	+39.6	31	42	−11	11.1	8.6	+2.5
Exudative lesions	69	100	100	0	90	49.4	+40.6	45	42	+3	10.1	8.6	+1.5
Fibrotic lesions	51	100	100	0	86	49.4	+36.6	41	42	−1	13.7	8.6	+5.1
Cavitation	23	100	100	0	91	49.4	+41.6	65	42	+23	8.6	8.6	0
Lesions of the upper lobe	78	100	100	0	89	49.4	+39.6	45	42	+3	8.9	8.6	+0.3
Lesions of the lower lobe	14	100	100	0	79	49.4	+29.6	36	42	−6	21.4	8.6	+12.8
Splenomegaly	5	100	100	0	100	49.4	+50.6	40	42	−2	0	8.6	0
Hepatomegaly	3	100	100	0	100	49.4	+50.6	33	42	−9	0	8.6	0
Generalized lymphadenopathy	54	100	100	0	87	49.4	+37.6	43	42	+1	12.9	8.6	+4.3
Positive sputum	11	100	100	0	100	49.4	+50.6	45	42	+3	0	8.6	0

the reaction to tuberculin became positive were discharged on a certificate of disability with the diagnosis of minimal, arrested pulmonary tuberculosis. It is impossible to say whether these 4 patients became infected while in the hospital or whether they were for some unknown reason anergic to tuberculin for the first seven to nine months and later became sensitive for a still unknown reason. For the 7 patients who gave a negative reaction to tuberculin the following type of diagnosis was made: pulmonary fibrosis (lobe involved), cause undetermined, characterized by roentgenologic evidence of parenchymal infiltration (of lobe involved), with normal sputum, negative reactions to the tuberculin cutaneous test and strong sensitivity of the skin to histoplasmin. These patients were sent to duty except in a few instances in which they were discharged from the Service for other reasons.

COMMENT

The problem which initiated this study was one of the differential diagnosis of pulmonary pathema discovered on routine roentgen examination of soldiers being separated from the service. While it is recognized that nontuberculous processes may exist simultaneously in patients with proved tuberculosis, we were not greatly concerned with the patients who presented a typical roentgen picture of tuberculosis and whose sputum contained acid-fast bacilli. Even patients with typical roentgen findings and a positive cutaneous reaction to the tuberculin test in the absence of acid-fact bacilli in the sputum caused little concern in arriving at a presumptive diagnosis, even though we were conscious of the inadequate criteria for such a diagnosis. However, patients with typical roentgen findings and with no sensitivity of the skin to tuberculin were extremely perplexing. Bronchoscopic examinations were made frequently, and a tremendous amount of laboratory work was done for many of them. The behavior of the lesion as observed by serial roentgenograms was frequently of no specific assistance in the etiologic diagnosis. While the battery of skin tests with tuberculin, coccidioidin and histoplasmin was actually of no help in the differential diagnosis, certain interesting observations were made.

The reference to table 1 shows at a glance that the majority of patients gave a weakly positive reaction to all three of the antigens. When the three tests were done simultaneously the patients were observed to fall into one of several sensitivity groups, depending on the combination of sensitivities exhibited at the time. For instance, group 1 is composed of patients who were sensitive to tuberculin, coccidioidin and histoplasmin, group 2 of patients who were sensitive to tuberculin and coccidioidin, group 3 of patients sensitive to tuberculin and histoplasmin and group 4 of patients sensitive to coccidioidin and histoplasmin. Groups 5, 6 and

7 are composed of patients sensitive to tuberculin only, coccidioidin only and histoplasmin only in the order named. With reference to figure 1, it is immediately apparent that 96.6 per cent of a group of 528 patients gave positive reactions to tuberculin (section *A*), while 3.4 per cent gave negative reactions. Fifty-eight and three-fifths per cent were sensitive to histoplasmin (section *B*) and 31.1 per cent were sensitive to coccidioidin (section *C*). Three patients with positive reactions to the coccidioidin and tuberculin tests of the skin were found to have both acid-fast organisms and the spherules of Coccidioides in their bronchial secretions simultaneously. In no instance were we able to isolate H. capsulatum from the sputum, from lymph nodes or from cultures of the bone marrow in patients with a positive reaction to histoplasmin. Extremely careful mycologic studies were made of all the patients with a sensitivity of the skin to histoplasmin, and it is felt that the presence of viable forms of H. capsulatum was ruled out in the tissues examined. While the incidence of sensitivity to one single fungus antigen without concomitant sensitivity to tuberculin was rare, being 1.7 per cent for histoplasmin and 0.6 per cent for coccidioidin, 33.9 per cent of the patients were sensitive to tuberculin only.

In table 2 the patients are divided into three groups. Four hundred and ninety-one, or 93 per cent, were sensitive to tuberculin, 48 per cent were sensitive to histoplasmin and 30 per cent were sensitive to coccidioidin. None of these groups is completely homogeneous, as of the group sensitive to tuberculin 32 per cent were also sensitive to histoplasmin; 6 per cent to coccidioidin and 24 per cent to both histoplasmin and coccidioidin. In the group with sensitivity to histoplasmin, 32.5 per cent were also sensitive to tuberculin and 24.1 per cent to tuberculin and coccidioidin. In the group sensitive to coccidioidin, 6.1 per cent were sensitive to tuberculin and 24.1 per cent to tuberculin and histoplasmin. Certain roentgenologic and physical findings were tabulated as they occurred in each of the three groups. These are shown in table 2. The clinical factors are listed in the left margin, column 1 showing the number of patients exhibiting each. Columns 2, 6 and 10 show the number of patients in each group with these clinical factors. Columns 4, 8 and 12 show the incidence of each factor that would be expected if based on a pure mathematical ratio of each group. The standard deviation of these percentages varied from 1.5 to 3. Columns 5, 9 and 13 show the difference between the observed and the expected occurrence of each of the clinical factors. Column 5 shows that there is no greater occurrence of any of the clinical factors in the group sensitive to tuberculin than would be expected from a computation based on the pure arithmetic ratio of the population of the group. However, less than the expected number of patients with pain in the chest and with

hepatomegaly were included in his group. In the group sensitive to histoplasmin, there were 12 per cent more than the expected number with hilar calcification and 14.6 per cent more than the expected number with parenchymal calcification. It is interesting to note that 14 per cent more than the expected number had exudative pulmonary lesions in the group sensitive to histoplasmin. In this respect it should be pointed out that 7 patients with a positive reaction to histoplasmin and a negative reaction to tuberculin exhibited an exudative lesion in the upper lobes of the lungs, which progressed for two or three months and then finally regressed and became stationary. These lesions behaved exactly as would have been expected of a minimal tuberculosis lesion in the apexes. However, acid-fast bacilli were never obtained from the sputum of these patients even on bronchoscopic examination and the reaction to the tuberculin test of the skin was negative even with the use of 0.1 mg. of purified protein derivative. In the group sensitive to coccidioidin there was no great difference between the expected and the observed occurrence of any of the clinical factors listed.

Of the 528 patients followed for six months or longer, 167 were found to have pulmonary calcification. Table 3 shows the distribution of these patients with reference to their cutaneous sensitivity. Only 15.3 per cent of the 209 patients who were sensitive to tuberculin had pulmonary calcification. Of these, 5.5 per cent had hilar calcifications and 13.4 per cent had parenchymal calcifications. Of the group sensitive to tuberculin and coccidioidin, 31 per cent showed evidence of pulmonary calcification, and of the group sensitive to tuberculin and histoplasmin, 39 per cent had such evidence. In 13 per cent the calcification was in the hilar region and in 23 per cent in the parenchymal zones. Of the 10 patients with sensitivity to histoplasmin only 7, or 70 per cent, showed pulmonary calcification; in 20 per cent it was in the hilar region and in 50 per cent in the parenchymal zones. Of the 21 patients with negative reactions to all three antigens, 33 per cent showed pulmonary calcification; in 19.3 per cent the calcifications were hilar and in 14.3 per cent parenchymal. These figures are not at all unusual when it is considered that most of the patients sensitive to tuberculin had minimal tuberculosis and that calcification from coccidioidomycosis has been known for some time.[5] The occurrence of calcified pulmonary lesions in persons sensitive to histoplasmin agrees with the implication made by Palmer, Christie and others that calcified pulmonary lesions are frequently seen in such persons.

About 60 per cent of the 528 patients had sensitivity of the skin to histoplasmin. The distribution of these patients by states is given in table 4 and graphically represented on the spot map in figure 2. The

5. Aronson, J. D.; Saylor, R. M., and Parr, E. I.: Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, Arch. Path. **34**:31-48 (July) 1942.

tabulation and spot map show that there is a fairly even distribution of positive and negative reactors. These include all patients reacting to histoplasmin, including those with a relatively mild degree of sensitivity, characterized by a 5 to 10 mm. area of induration and erythema, as well as those with a severer reaction, characterized by an area of 20 mm. and above. In view of the knowledge of cross sensitivity reactions between histoplasmin, haplosporangin, blastomycin, coccidioidin and probably preparations from several other fungi, this suggests the distribution that one would expect. However, if the distribution of only patients with a relatively strong sensitivity to histoplasmin is studied, the results are those indicated in figure 3 and table 6. In table 6 all patients with a sensitivity to histoplasmin indicated by an area of more than 20 mm.

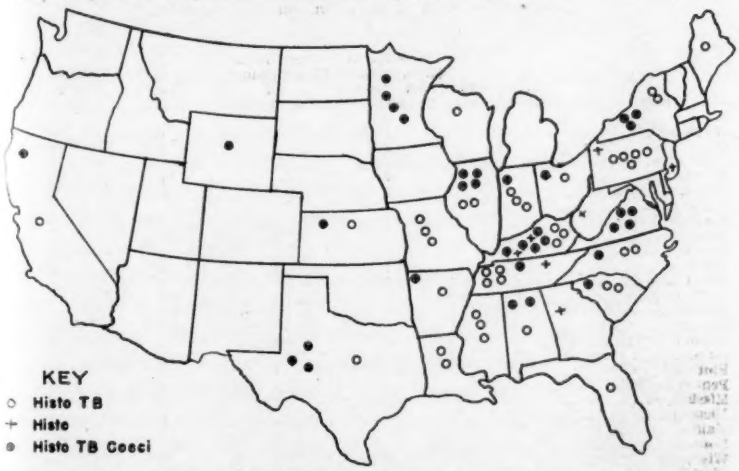

Fig. 3.—Spot map of the United States, showing distribution of 81 patients with strong reactions to histoplasmin (20 mm.) and to tuberculin and coccidioidin.

of erythema and induration are listed. Twelve per cent of the patients from Kentucky and 7 per cent of the patients from Tennessee, Illinois and Pennsylvania exhibited a more or less pronounced sensitivity. In figure 3 the open circles represent patients sensitive to histoplasmin and tuberculin. The plus marks indicate those sensitive to histoplasmin only. The circle inclosing the plus mark indicates sensitivity to histoplasmin, tuberculin and coccidioidin.

Eighty-one patients with a strong reaction to histoplasmin were selected for special study. These patients all reacted with an area of induration and erythema measuring more than 20 mm. The characteristics of the roentgenologic findings and the incidence of splenomegaly, hepatomegaly and generalized lymphadenopathy and of the occurrence of acid-fast organisms in the sputum are given in table 5. The clinical

factors are listed in the left margin. Column 1 shows the number of patients in the group exhibiting each clinical factor listed. The combinations of sensitivity to histoplasmin as related to sensitivity to tuberculin and to coccidioidin are indicated in the top horizontal column. Forty persons were sensitive to histoplasmin and tuberculin, comprising 49.4 per cent of the total of 81. Among them were found 89 per cent of the patients with pulmonary calcification, 90 per cent of those with exudative lesions and 86 per cent of those with fibrotic pulmonary lesions. Also included were 91 per cent of the patients with cavitation as well

TABLE 6.—*Geographic Distribution of Eighty-One Patients with Strong Positive Reactions of the Skin (20 mm. and over) to Histoplasmin Alone and in Combination with Tuberculin and Coccidioidin*

State	Sensitive to Histoplasmin	Sensitive to Histoplasmin, Tuberculin and Coccidioidin	Sensitive to Histoplasmin and Tuberculin	State Total	Percentage of State Total
Wyoming	..	1	..	1	1
Tennessee	1	1	4	6	7
California	..	1	1	2	2
Minnesota	..	4	..	4	5
Alabama	..	2	1	3	4
Indiana	..	1	3	4	5
Virginia	..	4	..	4	5
Kentucky	2	5	3	10	12
Texas	..	3	1	4	5
Arkansas	..	1	1	2	2
New York	..	3	2	5	6
North Carolina	..	1	2	3	4
Illinois	..	4	2	6	7
Kansas	..	1	1	2	2
South Carolina	..	1	2	3	4
Ohio	..	1	1	2	2
Florida	..	..	1	1	1
Pennsylvania	1	..	5	6	7
Mississippi	..	..	3	3	4
Missouri	..	..	3	3	4
Maine	..	..	1	1	1
Louisiana	..	..	2	2	2
Wisconsin	..	..	1	1	1
West Virginia	1	..	..	1	1
New Jersey	1	..	..	1	1
Georgia	1	..	..	1	1

as all the patients with splenomegaly, hepatomegaly and sputum containing acid-fast organisms. The group of 40 included all patients with a sensitivity to histoplasmin and tuberculin regardless of whether they were sensitive to coccidioidin. In the next group, comprising those sensitive to histoplasmin and coccidioidin, there were 34, or 42 per cent of the total group. These were all patients who were sensitive to histoplasmin and coccidioidin regardless of whether they were sensitive to tuberculin. The group of 7 persons sensitive to histoplasmin only, comprising 8.6 per cent of the total group, included 11.1 per cent of the patients with pulmonary calcification. Ten per cent of those with exudative lesions, 13 per cent of those with fibrotic lesions and 21 per cent of those with lesions of the lower lobes fell in this group. Twelve

per cent of the patients with generalized lymphadenopathy also were in this group.

It must be remembered that the presence of pulmonary calcification may be due to a great number of etiologic agents. Roentgenologic evidence of any pulmonary pathema, whether fibrotic, exudative or calcific, calls for the most thorough elicitation of the patient's history and for thorough physical examination as well as for bacteriologic and mycologic studies. However, the sensitivity of the skin to certain antigens such as tuberculin and coccidioidin may at times furnish valuable bits of information to assist in the arrival at the final diagnosis. In the use of the sensitivity of the skin to histoplasmin in the differential diagnosis of pulmonary pathema, one must consider several factors: (1) the known cross sensitivity reactions, (2) the strength of the reaction, (3) the possibility of the existence of a benign infection with H. capsulatum and (4) the possibility of a sensitivity reaction secondary to therapy with the antibiotics. One of the patients in this series who originally gave a negative reaction to histoplasmin showed an area of reaction of 10 mm. to a 1 to 1,000 dilution after he had received a course of penicillin for syphilis. The patient had a rather severe urticarial reaction to the penicillin. No explanation for the newly acquired sensitivity to histoplasmin was found.

Histoplasmosis is at present considered to be uniformly fatal; however, cases have been reported [8] in which H. capsulatum has been recovered from patients in whom histoplasmosis was not the cause of death. It is not known whether these patients would have died ultimately as a result of the infection with H. capsulatum or whether the outcome would have been similar to that in the Rhesus monkey infected by Wright and Hachtel in 1941.[6] This animal was infected with H. capsulatum after which several blood cultures which yielded the organism were obtained. When the animal was finally killed, autopsy revealed no evidence of the organism. In DeMonbreun's work, the Rhesus monkeys all died of the infection.[7] McLeod [8] reported 2 cases of fatal histoplasmosis in which the reaction to the test with histoplasmin was negative. Christie [8] reported a case of fatal histoplasmosis in an infant in whom the reaction to the skin test was positive; the patient's mother and father were also sensitive to histoplasmin.

Evidence so far presented in the literature seems to indicate the possibility of a benign self limiting infection with H. capsulatum which

6. Wright, R. B., and Hachtel, F. W.: Histoplasmosis of Darling: Report of a Case, Ann. Int. Med. **15**:309-319, 1941.

7. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's Histoplasma Capsulatum, Am. J. Trop. Med. **14**:93-125, 1934.

8. McLeod, J. H.; Emmons, C. W.; Ross, S., and Burke, F. G.: Histoplasmosis, J. Pediat. **26**:275-295, 1946.

is associated with complete recovery, a high incidence of pulmonary calcification and a sensitivity of the skin to histoplasmin. Further study with experimental animals will undoubtedly shed some light on this subject.

The presence of a benign type of histoplasmosis is of academic interest but not of great importance to physicians dealing with thoracic diseases. On the basis of the present knowledge of pulmonary disease, the most crying need is for an accurate method of determining the presence of tuberculosis in patients with undiagnosed pulmonary pathema. While a patient may have a sensitivity of the skin to a multitude of antigens, among them histoplasmin, his pulmonary pathema may be the result of an infection with Paragonimus westermani or may be some other equally rare condition. A positive reaction to the Mantoux test may have no connection with the abnormal shadow in the roentgenogram under consideration at the moment.

At the present time there is no certainty that the patient with pulmonary disease has tuberculosis unless the tubercle bacilli is demonstrated in the sputum or bronchial secretions or cultured from gastric washings. Even with this evidence, patients with tuberculosis may have additional infections, such as coccidioidomycosis or other fungous diseases or tropical diseases, which must be discovered if scientific therapy is to be instituted.

Ogden and associates [9] have introduced a method of study employing the tuberculocomplement fixation test in combination with Caulfeild's "inhibitive test" and the Mantoux test, which they claim to be of great diagnostic and prognostic value in the treatment of pulmonary tuberculosis. While Caulfeild's work has been almost universally rejected, it is possible that the addition of some similar method of study will greatly improve our diagnostic acumen in pulmonary disease.

SUMMARY

1. Skin tests with a battery of three antigens—tuberculin, histoplasmin and coccidioidin—were made on 1,220 patients with roentgen evidence of pulmonary pathema compatible with that of pulmonary tuberculosis. Ninety-six and three-fifths per cent were sensitive to tuberculin, 58.6 per cent were sensitive to histoplasmin and 31.1 per cent were sensitive to coccidioidin.

2. Seven patients in the group were strongly sensitive to histoplasmin and gave negative reactions to tuberculin (0.1 mg. of purified protein derivative) and coccidioidin. The lesions in all 7 were similar, with characteristics of tuberculosis, except for the absence of acid-fast bacilli in the bronchial secretions and of sensitivity to tuberculin.

9. Ogden, A., and others: Foreseeing and Forestalling Tuberculosis, Dis. of Chest **12**:277-329, 1946.

3. Efforts to isolate a fungus characteristic of Histoplasma capsulatum by microscopic examination and careful mycologic studies of bone marrow, sputum and lymph nodes of the patients with a strong sensitivity of the skin to histoplasmin were consistently nonproductive.

4. Patients with a strong reaction to histoplasmin in a 1 to 1,000 dilution usually showed a mild reaction to coccidioidin in a 1 to 10 dilution; those with a strong reaction to coccidioidin in the 1 to 1,000 dilution usually had a mild reaction to the 1 to 1,000 dilution of histoplasmin. This cross sensitivity reaction is also suggested by the geographic distribution of patients with and without sensitivity to histoplasmin (fig. 2).

5. There was a considerable difference in the geographic distribution of those with strong reactions to histoplasmin as compared to those with mild reactions (with areas of reaction of 5 and 10 mm.) (figs. 2 and 3).

6. The incidence of pulmonary calcifications was greater in the group sensitive to histoplasmin than in the groups sensitive to coccidioidin or tuberculin.

7. Of 528 patients for whom a presumptive diagnosis of pulmonary tuberculosis was made by roentgen studies, 117 were found to have acid-fast bacilli in their bronchial secretions or in gastric washings.

8. The diagnosis of pulmonary tuberculosis was made for 404 patients with only the following evidence of this disease: (*a*) characteristic roentgen evidence of pulmonary pathema and (*b*) sensitivity of the skin to tuberculin.

9. For 7 patients with no sensitivity of the skin to tuberculin the diagnosis of pulmonary fibrosis, cause undetermined, was made.

CONCLUSIONS

In the light of the present knowledge of histoplasmosis, the use of the test of sensitivity of the skin to histoplasmin is of limited value in the differential diagnosis of pulmonary disease.

In a group of patients with roentgen evidence of tuberculosis, 93.6 per cent were sensitive to tuberculin, 58.6 per cent were sensitive to histoplasmin and 31.1 per cent were sensitive to coccidioidin. Both histoplasmosis and coccidioidomycosis are known to leave pulmonary pathema similar to that of tuberculosis. Therefore, more exacting criteria for the diagnosis of pulmonary tuberculosis should be available than those of roentgenologic studies and sensitivity of the skin to tuberculin.

The Caulfeild inhibitive test in combination with the tuberculo-complement fixation test or some similar method such as the agglutination test may prove to be essential in the exact diagnosis of minimal tuberculosis in the future.

The present methods used in the differential diagnosis of pulmonary tuberculosis are inadequate.

Progress in Internal Medicine

INFECTIOUS DISEASES

Thirteenth Annual Review of Significant Publications

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Papers published during the past year dealing with infectious diseases contain no spectacular report such as readers have become accustomed to expect in recent times. Except for encouraging effects of streptomycin in tuberculosis, the synthesis of penicillin, information that under certain conditions both penicillin and streptomycin actually stimulate bacterial growth and the inhibiting effect of certain other antibiotics on neoplastic cells, studies in the field of antibiotics have been in the nature of odds and ends. The sulfonamide compounds are found to be of less and less use and are obsolete for many conditions. Interest in viral hepatitis and viral pneumonia has waned apparently in proportion to the decrease in the incidence of these infections consistent with the natural rise and fall of epidemic diseases. A new rickettsial disease was discovered in New York city.

The feasibility of biologic warfare based on facts and theory at hand up to 1942 was discussed in an eighty page paper.[1] One wonders if so long a paper is justified if much or all of the pertinent information gleaned in intensive study since 1942 is withheld. Reading it leaves a feeling that the chances of success in causing serious human epidemics are poor unless, of course, they are started in regions devastated by natural or artificial catastrophies in which natural and technical defensive measures are inoperative. It is comforting to recall that the concatenation of numerous known and unknown factors essential to cause an epidemic is a fortuitous one which it is almost impossible to achieve deliberately. About thirty diseases of human beings are listed as possible offensive weapons. Among them is bacillary dysentery, but elsewhere in the present review the difficulty of causing dysentery even in volunteers who drank heavy inoculums of bacilli is cited. Because air-borne infections frequently cause accidental infection among laboratory workers who handle the causative agents or are exposed to them, these also have been considered. Among them are tularemia, yellow

From the Jefferson Medical College and Hospital.

1. Rosebury, T.; Kabat, E. A., and Boldt, M. H.: Bacterial Warfare: A Critical Analysis of the Available Agents, Their Possible Military Application, and the Means for Protection Against Them, J. Immunol. **56**:7-96 (May) 1947.

fever, louping ill, Q fever, influenza and coccidioidomycosis, yet in no instance of the infections just mentioned or of the following ones did disease spread farther.

LABORATORY INFECTIONS

Laboratory infections with glanders, poliomyelitis and plague are referred to later in these pages. Rosebury [2] describes instances of psittacosis, and Haedlicke [3] reports 4 cases in which typhoid was contracted by vaccinated persons working with cultures. The disease was described as so mild as to make diagnosis difficult, yet the charts in all 4 cases showed temperatures of 40 C. (104 F.) and the disease lasted from four to seven weeks. Sadusk [4] observed cases in which typhus was probably contracted by the inhalation of rickettsia-bearing dust in laboratories, and Howe [5] describes 17 cases of accidentally acquired brucellosis. Sabin himself contracted Rift Valley fever,[6] and accidental infections have occurred in practically every laboratory in which the disease was studied. Four laboratory workers had Venezuelan equine encephalomyelitis while working with the disease.[6a]

ANTIBIOTICS

The historic and theoretic aspects of chemotherapy and antibiotic therapy are presented in a series of articles in the *British Medical Bulletin* (**40**: 4, 1946) and in an essay by Florey.[7]

According to a report,[8] Chain, one of the developers of penicillin, predicted that synthetic penicillin would never replace the natural product "unless someone invented an entirely new technic unlike anything which now is known in chemistry." Soon afterward, duVigneaud [9]

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2. Rosebury, T.; Ellingson, H. V., and Meiklejohn, G.: A Laboratory Infection with Psittacosis Virus Treated with Penicillin and Sulfadiazine, J. Infect. Dis. **80**:64-77 (Jan.-Feb.) 1947.

3. Haedlicke, T. A.: Typhoid Fever in Vaccinated Laboratory Workers, J. Infect. Dis. **80**:113-116 (Jan.-Feb.) 1947.

4. Sadusk, J. F.: Typhus Fever in the United States Army Following Immunization, J. A. M. A. **133**:1192-1199 (April 19) 1947.

5. Howe, C., and others: Acute Brucellosis Among Laboratory Workers, New England J. Med. **236**:741-747 (May 15) 1947.

6. Sabin, A. B., and Blumberg, R. W.: Human Infection with Rift Valley Fever Virus and Immunity Twelve Years After Single Attack, Proc. Soc. Exper. Biol. & Med. **64**:385-389 (April) 1947.

6a. Koprowski, H., and Cox, H. R.: Human Laboratory Infections with Venezuelan Equine Encephalitis Virus: Report of Four Cases, New England J. Med. **236**:647-653 (May 1) 1947.

7. Florey, H. W.: The Use of Micro-Organisms for Therapeutic Purposes, Yale J. Biol. & Med. **79**:101-117 (Oct.) 1946.

8. The Merck Report, October 1946.

9. du Vigneaud, V.; Carpenter, F. H.; Holley, R. W.; Livermore, A. H., and Rachele, J. R.: Synthetic Penicillin, Science **104**:431-433 (Nov. 8) 1946.

announced the synthesis of penicillin. There is no indication at present, however, that this accomplishment will allow production of synthetic penicillin on a commercial basis, but the way is opened for the possible development of new compounds which may even exceed penicillin in therapeutic value.

In a series of papers in the February issue of the *Journal of Experimental Medicine* Eagle writes that penicillin F, G, K and X are all inactivated to some degree by serum by two distinct mechanisms. In the slow inactivation penicillin X was least affected. By the more important rapid factor penicillin K alone was inactivated, especially when it was present in small amounts. The highest sustained amount in the blood was afforded by penicillin X and the lowest by K. Furthermore, although efforts now are made commercially to obtain a high proportion of penicillin G in the products used for treatment, penicillin X is twice as effective as penicillin G against pneumococci, streptococci and gonococci. These facts, in addition to its slower inactivation by serum, would seem to make penicillin X the one of choice.

Others [9a] interpret the differences in the amount of penicillin fractions in the blood on the basis of their difference in degree of binding with proteins of the serum. Evidence is given to show that the previous findings of larger and more prolonged amounts of penicillin X in the blood and the lower amounts and rapid disappearance of penicillin K were artefacts caused by the action of serum during the process of assaying. Therefore, differences in the therapeutic effectiveness of the various fractions of penicillin cannot be explained by the differences in the amount and duration as measured in the blood.

Penicillin rapidly deteriorates when mixed with glycerin, propylene glycol and other viscous agents. Stability also varies with the particular salt used in the preparation.[10]

Important observations indicate that in low concentration both penicillin and streptomycin, like certain drug and chemical agents, serve as stimulants to bacterial growth [10a] but in large amounts they are deterrents. Curran and Evans [11] show how small amounts of anti-

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9a. Tompsett, R.; Shultz, S., and McDermott, W.: Influence of Protein-Binding on the Interpretation of Penicillin Activity in Vivo, Proc. Soc. Exper. Biol. & Med. **65**:163-172 (June) 1947.

10. Ferlauto, R. J., and Clymer, H. A.: Stability of Penicillin in Glycerin and Glycols, Science **105**:130-131 (Jan. 31) 1947.

10a. Acquired Resistance to Penicillin, Annotation, Brit. M. J. **2**:101-102 (July 19) 1947.

11. Curran, H. R., and Evans, F. R.: Stimulation of Sporogenic and Non-sporogenic Bacteria by Traces of Penicillin or Streptomycin, Proc. Soc. Exper. Biol. & Med. **64**:231-233 (Feb.) 1947.

biotic agents increase the growth rate of certain strains of staphylococci and streptococci, and because of this, they emphasize the danger of using antibiotics therapeutically in subeffective dosage. In other studies,[12] exposure of strains of Hemophilus influenzae to penicillin gave rise to the appearance of pleuropneumonia-like bacilli.

Although most physicians favor the intrathecal injection of penicillin in addition to intramuscular injection for meningitis, I have felt that the latter is sufficient. Now comes report [13] of spinal arachnoiditis, transverse myelitis and injury to the brain after intraspinal injection. The authors recommend early parenteral injection of maximum doses of penicillin as preferable to intraspinal injection.

In two papers [14] published in abstract, report is made of the effect of caronamide (4′-carboxyphenylmethanesulfonanilide) given orally on the amount of penicillin in the blood. The substance delays the excretion of penicillin by the renal tubules and thereby increases the amount retained in the blood from two to seven times. It seems questionable whether such a procedure is worth the risk of possible harm when levels in the blood attained with the usual doses are adequate for most purposes. More detailed studies are published elsewhere.[14a]

Streptomycin.—Older information on the subject is reviewed adequately elsewhere.[15]

Intensive studies on the effect of streptomycin on tuberculosis are in progress. Reports are favorable to the extent that streptomycin appears to suppress tuberculous infection rather than to eradicate it. The drug is bacteriostatic and not bactericidal in the amounts in which it reaches the tissues. Treatment requires large dosage over long periods and is subject to toxic side effects. As an indication of the great interest in the matter, the use of streptomycin for tuberculosis is discussed in abstract form by six groups of investigators in the program of the 1947 meetings of the American Society for Clinical Investigation. All report strikingly favorable effects. There was

12. Dienes, L.: Isolation of Pleuropneumonia-like Organisms from H. Influenzae with the Aid of Penicillin, Proc. Soc. Exper. Biol. & Med. **64**:166-168 (Feb.) 1947.

13. Erickson, T. C.; Masten, M. G., and Suckle, H. M.: Complication of Intrathecal Use of Penicillin, J. A. M. A. **132**:561-565 (Nov. 9) 1946.

14. Boger, W. P., and others: High Penicillin Plasma Concentration by the Use of Caronamide, a Compound that Inhibits Penicillin Excretion by the Renal Tubules, paper read before the American Society for Clinical Investigation, May 5, 1947. Parker, R. F., and Albright, R.: The Effect of Caronamide in Inhibiting Penicillin Excretion, ibid.

14a. Crosson, J. W., and others: Caronamide for Increasing Penicillin Plasma Concentration in Man, J. A. M. A. **134**:1528-1532 (Aug. 30) 1947.

15. Murray, R.; Paine, T. F., and Finland, M.: Streptomycin, New England J. Med. **236**:701-712 (May 8); 748-760 (May 15) 1947.

prompt disappearance of ulcerative lesions of the trachea and bronchi but only temporary symptomatic improvement of other lesions in the lungs. Draining tuberculous sinuses healed with one to twenty weeks of therapy. In Bunn's report of 6 patients with miliary or meningeal tuberculosis, 4 were apparently cured. Complete clearing of the miliary lesions occurred roentgenographically. The dosage varied from 1.2 to 4 Gm. daily often for as long as one hundred and twenty days. D'Esopo's group noted resolution "to a greater or lesser extent" in 77 per cent of 120 patients with far advanced pulmonary tuberculosis treated for four months. No new lesions developed during the course of treatment, nor did lesions progress. Therapy is most effective for exudative lesions and is suppressive rather than definitive. In the program and elsewhere [16] Hinshaw and Feldman added further favorable evidence to their previous data and concluded that the permanence of the good results depends on how much natural healing occurs before the tubercle bacilli become resistant to streptomycin. In the experience of McDermott and his co-workers, therapy was continued in some patients for three hundred days. Resistance of the bacilli to streptomycin developed after the fourth week in most cases, and relapse often occurred when that took place. Toxic effects from streptomycin usually accompanied prolonged therapy.

Some observers [17] are pessimistic about the curative effects of streptomycin, since in clinical tuberculosis the bacilli appear to reproduce at long irregular periods undeterminable by any means and it is possible to provide an adequate amount of the drug in the tissues for only brief periods. Furthermore, there is no evidence that streptomycin enters important organs in appreciable amounts over long periods. The clinical value of streptomycin in tuberculosis, they feel, is limited.

Streptomycin together with type-specific antiserum and sulfadiazine is recommended for the treatment of meningitis caused by H. influenzae [18] for the following reason.[19] Cultures of H. influenzae almost always contain small numbers of bacilli which are probably variant forms and are highly resistant to streptomycin. All sensitive bacilli are eliminated by growth in medium containing streptomycin, but since the remaining resistant ones are sensitive to sulfadiazine both agents

16. Hinshaw, H. C.; Feldman, W. H., and Pfuetze, K. H.: The Treatment of Tuberculosis with Streptomycin: A Summary of Observations on One Hundred Cases, J. A. M. A. **132**:778-782 (Nov. 30) 1946; Streptomycin in Treatment of Clinical Tuberculosis, Am. Rev. Tuberc. **54**:191-203 (Sept.) 1946.

17. Corper, H. J., and Cohn, M. L.: The Tubercle Bacillus and Fundamental Chemotherapeutic and Antibiotic Action, Yale J. Biol. & Med. **19**:1-22 (Oct.) 1946.

18. Alexander, H. E.: Streptomycin in Pediatrics, J. Pediat. **29**:192-202 (Aug.) 1946.

19. Alexander, H. E., and Lindy, G.: Mode of Action of Streptomycin on Type b Hemophilus Influenzae, J. Exper. Med. **85**:607-621 (June) 1947.

should be used in therapy. In Logan and Herrell's [20] experience with these three agents, improvement in 2 patients did not occur until streptomycin was used. Streptomycin alone is curative in mild or moderately severe attacks. In most reports of the treatment of this heretofore almost invariably fatal disease, the mortality rate has been greatly diminished by the use of streptomycin.

Streptomycin was used with success in the treatment of 11 patients with tularemic pneumonia [21] and in pneumonic plague. It was also of value in 8 cases of bacillary dysentery when given orally and parenterally in doses of 1 to 4 Gm. daily for three to sixteen days.[22] Four patients with gonorrheal urethritis were successfully treated with 0.1 Gm. of streptomycin at hourly intervals for five doses.[22a]

A review of the literature concerning infections caused by Bacillus pyocyaneus and studies of the effect of streptomycin on them has been presented.[23] According to the author, this infection is becoming more common because of the suppression of other competitively invasive bacteria by chemical and antibiotic agents. Harris and others [24] obtained good results in 50 per cent of patients with infection of the urinary tract, especially when the urine was kept alkaline. Finland's group [25] report good results in only 4 of 12 cases. The failures were apparently due to the development of resistance to streptomycin on the part of the causative bacteria.

Certain patients with pneumonia caused by H. influenzae or by Friedländer's bacili were greatly benefited by streptomycin, and others were not.[26] Resistance against streptomycin developed by the causative bacteria appears to be a factor in poor therapeutic results in some cases.

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20. Logan, G. B., and Herrell, W. E.: Streptomycin in the Treatment of Influenzal Meningitis of Children, Proc. Staff Meet., Mayo Clin. **21**:393-400 (Oct. 16) 1946.

21. Hunt, J. S.: Pleuropulmonary Tularemia: Observations on Twelve Cases Treated with Streptomycin, Ann. Int. Med. **26**:263-276 (Feb.) 1947.

22. Pulaski, E. J., and Anspacher, W. H.: Streptomycin in Intestinal Infections, Bull. U. S. Army M. Dept. **6**:750-760 (Dec.) 1946.

22a. Chinn, B. D., and others: Treatment of Gonorrhea with Streptomycin, Am. J. Syph., Gonor. & Ven. Dis. **31**:268-270 (May) 1947.

23. Stanley, M. M.: Bacillus Pyocyaneus Infections: A Review; Report of Cases and Discussion of New Therapy Including Streptomycin, Am. J. Med. **2**:253-277 (March); 347-367 (April) 1947.

24. Harris, H. W., and others: Streptomycin Treatment of Urinary Tract Infections, with Special Reference to the Use of Alkali, Am. J. Med. **2**:229-250 (March) 1947.

25. Finland, M., and others: Development of Streptomycin Resistance During Treatment, J. A. M. A. **132**:16-21 (Sept. 7) 1946.

26. Harris, H. W.; Murray, R.; Paine, T. F., and Finland, M.: Streptomycin Treatment of Pulmonary Infections: Clinical and Bacteriologic Studies of Six Cases, New England J. Med. **236**:611-622 (April 24) 1947.

Twenty-three patients[27] with lymphogranuloma inguinale were benefited by daily doses of 0.3 to 1 Gm. of streptomycin and total dosages of 3.3 to 4.6 Gm. given over six to forty-five days, but relapses occurred. The authors regard streptomycin as the most effective remedy for the disease.

The reason for the failure of streptomycin to cure brucellosis caused by strains of Brucella highly sensitive to the drug in culture medium is unknown. Resistance to streptomycin, which develops in some but not in all strains of Brucella is not the only cause,[28] nor is the intracellular location of brucellas and of typhoid bacilli a tenable explanation of poor therapeutic results since Pasteurella tularensis is also present intracellularly yet the infection is controlled by streptomycin. The existence and persistence of streptomycin-resistant variant forms, as in the case of H. influenzae, dysentery bacilli[29] and meningococci,[30] offer a better explanation for therapeutic failure at present. It seems that variant or mutant forms resistant to streptomycin are constantly present in bacterial populations. Since many of these are virulent, they continue to grow and cause disease in the presence of the antibiotic, while the other drug-sensitive ones are suppressed.

A surprising discovery was reported by Miller and Bohnhoff[30] similar to that of Curran and Evans mentioned on a previous page. Certain variant forms of meningococci actually need streptomycin for growth. They were virulent for mice only in the presence of streptomycin. A strain of Staphylococcus was rendered resistant to three antibiotic preparations—after twelve transfers in medium containing streptomycin, after twenty-five transfers with streptothricin and after thirty-two with penicillin.[31] The resistance to one antibiotic did not result in increased resistance to the others.

Streptomycin has a slight inhibiting effect on typhus rickettsias grown in eggs, but paraaminobenzoic acid was much more suppressive.[32]

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27. Greenblatt, R. B., and others: Streptomycin in the Therapy of Granuloma Inguinale, Proc. Soc. Exper. Biol. & Med. **64**:389-390 (April) 1947.

28. Hall, W. H., and Spink, W. W.: In Vitro Sensitivity of Brucella to Streptomycin: Development of Resistance During Streptomycin Treatment, Proc. Soc. Exper. Biol. & Med. **64**:403-406 (April) 1947.

29. Klein, M., and Kimmelman, L. J.: The Role of Spontaneous Variants in the Acquisition of Streptomycin Resistance by the Shigellae, J. Bact. **52**:471-479 (Oct.) 1946.

30. Miller, C. P., and Bohnhoff, M.: Development of Streptomycin-Resistant Variants of Meningococci, Science **105**:620-621 (June 13) 1947.

31. Sullivan, M.; Stahly, G. L., and Birkeland, J. M.: Reciprocal Sensitivities of Staphylococcus Aureus to Streptomycin, Streptothricin and Penicillin, Science **104**:397-398 (Oct. 25) 1946.

32. Morgan, H. R.; Stevens, D. A., and Snyder, J. C.: Effect of Streptomycin on Growth of Rickettsiae in Eggs, Proc. Soc. Exper. Biol. & Med. **64**:342-345 (March) 1947.

A combination of the two agents is more effective, as stated by Smadel at the Surgeon General's symposium in Washington, May 5, 1947.

Weinstein [32a] points out the danger of upsetting the balance of different pathogenic bacteria normally present in the body by the use of pencillin or streptomycin. Either agent may cure the primary disease by suppressing bacteria sensitive to their effects but may permit other resistant bacteria to multiply and become invasive, causing a new disease. Such infections may arise from bacteria already present but also from those introduced during the therapeutic procedure. Cases are reported in which infections with resistant H. influenzae, Klebsiella pneumoniae and staphylococci all caused serious disease in patients treated with penicillin or streptomycin for other infections.

The combined use of penicillin and streptomycin is condemed because of the occurrences just mentioned and of the possibility of sensitizing patients needlessly against either antibiotic. The use of antibotic therapy has increased rather than decreased the need for accurate and repeated bacteriologic diagnosis in the control of infectious diseases.

Other Antibiotics.—Meleney reports [33] further favorable results from local therapy of surgical infections with bacitracin, an antibiotic agent made by a gram-positive bacillus isolated from a patient named Tracey. The substance affects most of the bacteria sensitive to penicillin and some which are resistant to penicillin. It will be of importance only if it succeeds when other therapy fails.

A related antibiotic, subtilin, has a powerful therapeutic action against experimental infection with hemolytic streptococci in mice and against anthrax in guinea pigs.[34] Filtrates from cultures of certain molds, especially of Aspergillus terreus, inhibited the growth of Brucella abortus in high dilution.[35] Another antibiotic agent derived from California Spanish moss, a lichen (Ramalina reticulata), when given subcutaneously retards the progress of tuberculosis in guinea pigs infected with human tubercle bacilli.[36] In another study, glycerite of

32a. Weinstein, L.: The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin and Pencillin, Am. J. M. Sc. **214**:56-63 (July) 1947.

33. Meleney, F. L., and Johnson, B.: Bacitracin Therapy: The First Hundred Cases of Surgical Infections Treated Locally with the Antibiotic, J. A. M. A. **133**:675-680 (March 8) 1947.

34. Salle, A. J., and Jann, G. J.: Subtilin-Antibiotic Produced by Bacillus Subtilis: V. Effect on Streptococcus Pyogenes Infections in Mice, Proc. Soc. Exper. Biol. & Med. **63**:519-520 (Dec.) 1946; IV. Effect of Subtilin on the Course of Experimental Anthrax Infection in Guinea Pigs, ibid. **63**:41-42 (Oct.) 1946.

35. Beal, G. A.: Antibiotic Activity of Certain Molds Against Brucella, Proc. Soc. Exper. Biol. & Med. **64**:118-120 (Jan.) 1947.

36. Marshak, A.: A Crystalline Antibacterial Substance from the Lichen Ramalina Reticulata, Pub. Health Rep. **62**:3-19 (Jan. 3) 1947.

hydrogen peroxide applied as a wet dressing apparently favored the healing of long-standing tuberculous diseases.[37] Kidd [38] reports the suppressive effect of two antibiotic agents on tumor cells in cultural experiments.

INFECTIONS OF THE RESPIRATORY TRACT

If, as stated in textbooks, pandemics of influenza happen every thirty years, one is due next year. However, pandemics have been predicted repeatedly during the upheavals and hardships incident to the war, but none has come. Another pandemic of the magnitude of those of 1889 and 1918 probably will never recur unless some cataclysmic event disrupts the world or unless a new variant or mutant form of influenza virus becomes rampant. It is believed that the greatly increased intermingling of persons by extensive traveling has distributed various current influenza viruses and infections therewith so widely as to develop widespread partial immunity. Furthermore, in the event of a pandemic, the availability of specific therapeutic agents no doubt would greatly decrease the mortality rate from secondary pyogenic bacterial pulmonary infections.

Small epidemics of influenza B were reported from England [39] and the West Indies [40] synchronous with other outbreaks elsewhere in the world in 1945 and 1946. The strain varied somewhat from the standard Lee strain of B virus disease. Clinically, the disease was indistinguishable from influenza A. In Jackson's group [40] pneumonia occurred in 14 per cent of patients and was presumably caused by pneumococci. In influenza B observed in Rochester, N. Y., no benefit was noted from the prophylactic use of sulfadiazine.[41] Rales were heard in 4 of 46 cases, and the bronchial markings were intensified in 17 of 23 patients studied roentgenographically, indicating the frequency with which the lungs are involved. During another outbreak of influenza B, Leigh [42] studied a group of patients with neurologic disturbances presumably caused by the virus. Some had encephalitis resembling von

37. Brown, E. A., and Slanetz, L. W.: Antiseptic Action of Glycerite of Hydrogen Peroxide on Mycobacterium Tuberculosis (var. Hominis), Science **105**:312-313 (March 21) 1947.

38. Kidd, J. G.: Effects of an Antibiotic from Aspergillus Fumigatus Fresenius on Tumor Cells in Vitro, and Its Possible Identity with Gliotoxin, Science **105**:511-513 (May 16) 1947.

39. Dudgeon, J. A., and others: Influenza B in 1945-46, Lancet **2**:627-631 (Nov. 2) 1946.

40. Jackson, W. P. V.: Influenza B Among West Indians: Outbreaks in the Bahamas and in England, Lancet **2**:631-635 (Nov. 2) 1946.

41. Bruce, R. A., and Slavin, H. B.: A Study of an Outbreak of Influenza B in Rochester, N. Y., Am. J. M. Sc. **213**:129-134 (Feb.) 1947.

42. Leigh, A. D.: Infections of the Nervous System Occurring During an Epidemic of Influenza B, Lancet **2**:936-938 (Dec. 21) 1946.

Economo's lethargic type, as seen in 1918, and others had myelitis or polyneuritis. It was uncertain if the virus of influenza B was the cause or if another neurotropic virus was a secondary invader. With the knowledge that influenza viruses at times are neurotropic, there is reason to believe that influenza B virus was responsible.

Influenza Vaccine.—There is no doubt that influenza vaccines have prophylactic value against infection with homologous strains of influenza viruses. In Hirst's study [43] there were only 3 cases of influenza among 550 students vaccinated with a mixture of A and B influenza vaccine, as compared with 132 cases among 1,050 unvaccinated students, representing attack rates of about 0.5 and 12.5 per cent respectively.

In spite of the advantages of vaccine as exhibited in such carefully controlled studies, one wonders if vaccine as it is now prepared will be of practical value for general use under ordinary conditions against so mild a disease. There are at present at least four disadvantages, as follows:

A. Immunity conferred by actual disease is short, and immunity conferred by vaccine is even less complete and durable, as a rule lasting no longer than several months. Therefore, in any given season revaccination at intervals is needed. Furthermore, since epidemics are unpredictable the efforts and expense of vaccination are wasted if no epidemic appears. A dose of vaccine costs about one dollar.

B. Vaccines as now made are strain specific, and significant immunologic differences are known to exist even among strains of A virus. In Sugg's experiments,[44] animals infected with one A type virus were susceptible to reinfection with a different A type virus within four to ten weeks. In reports by Henle, Francis [44a] and Smadel [44b] and their co-workers, epidemics caused by a type A strain which differed immunologically from the strain used in the vaccine broke out shortly after vaccination. One wonders how many other different A or B strains may exist to cause similar failures.[44c]

43. Hirst, G. K.; Vilches, A.; Rogers, O., and Robbins, C. L.: The Effect of Vaccination on the Incidence of Influenza B, Am. J. Hyg. **45**:96-106 (Jan.) 1947.

44. Sugg, J. Y., and Magill, T. P.: Significance of Antigenic Differences Among Strains of Influenza A Virus in Reinfection of Ferrets, Proc. Soc. Exper. Biol. & Med. **63**:1-5 (Oct.) 1946.

44a. Francis, T.; Salk, J. E., and Quilligan, J. J.: Experience with Vaccination Against Influenza in the Spring of 1947, Am. J. Pub. Health **37**:1013-1016 (Aug.) 1947.

44b. Smadel, J. E.: Research in Virus Diseases, Bull. U. S. Army M. Dept. **7**:795-808 (Sept.) 1947.

44c. Francis, T.: Apparent Serological Variation Within a Strain of Influenza Virus, Proc. Soc. Exper. Biol. & Med. **65**:143-147 (June) 1947.

C. According to Salk and Francis [45] influenza vaccine causes local and systemic reactions similar to those occurring after antityphoid vaccination. In many cases the discomfort caused is greater than that from influenza itself.

D. Vaccine is now prepared in eggs, and since about 10 per cent of persons are allergic in general and 10 per cent of these are allergic to egg protein, it becomes necessary to exert caution when using vaccine to avoid serious and even fatal reactions.[46] Before injections of vaccine of this type, all recipients should be questioned for sensitivity or tested intradermally before each injection. This measure increases the labor and expense of mass vaccination but safely eliminates the small percentage (0.5 per cent) of persons in whom dangerous reaction may occur. Vaccines should be as free from egg protein as possible. Curphy reports [47] a fatal allergic reaction in a child of 3 vaccinated with A and B vaccine, caused either by the egg protein component or by the virus itself.

Burnet and his associates [48] discuss a "receptor gradient" in erythrocytes for the group of viruses causing mumps and influenza. Enzymes made by certain bacteria remove virus receptors by changing the surface character of the red cells so that they become less sensitive to clumping by viruses. Two theoretic implications arise: one, that enzymes play a role in the initial invasion of cells by viruses; the other, that the enzymatic effect may open the way to a new therapeutic approach.

In another study [49] Burnet and Anderson show how the virus of Newcastle disease of chickens clumps human erythrocytes as influenza virus does. Cells treated with the virus of the Newcastle disease develop a new antigenic character which makes them agglutinable with either Newcastle disease immune serum or serum from patients who had infectious mononucleosis. These effects suggest a new approach to the study of infectious mononucleosis.

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45. Salk, J. E., and Francis, T.: Immunization Against Influenza, Ann. Int. Med. **25**:443-452 (Sept.) 1946.

46. Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, J. A. M. A. **132**:899-905 (Dec. 14) 1946.

47. Curphy, T. J.: Fatal Allergic Reaction Due to Influenza Vaccine, J. A. M. A. **133**:1062-1064 (April 12) 1947.

48. Burnet, F. M.; McCrae, J. F., and Stone, J. D.: Modification of Human Red Cells by Virus Action: I. Receptor Gradient for Virus Action in Human Red Cells, Brit. J. Exper. Path. **27**:228-235 (Aug.) 1946.

49. Burnet, F. M., and Anderson, S. G.: II. Agglutination of Modified Human Red Cells by Serum from Cases of Infectious Mononucleosis, Brit. J. Exper. Path. **27**:236-243 (Aug.) 1946.

Influenza virus particles contain ribonucleic and desoxyribonucleic acids and carbohydrate-rich fractions of mannose, galactose and glucosamine units.[50]

Other Acute Diseases of the Respiratory Tract.—Modern knowledge of the minor ailments was reviewed by Reimann.[51] On clinical grounds, despite similarities several entities stand out, grouped as the common cold, nonbacterial pharyngitis, grip, febrile catarrh, viroid and influenza. In each of these real and supposed entities pneumonia occurs in a considerable number of patients, raising the question of whether it is caused by the same agent and is a severe form of the disease or by secondary bacterial invaders as a complication. The measures used for prevention and treatment are critically reviewed, and an outline of rational management is given.

In discussing one of the entities, nonbacterial exudative pharyngitis, members of the Commission on Acute Respiratory Diseases published information [52] which has already appeared in their other papers, namely, that a form of sore throat not caused by hemolytic streptococci commonly occurs. It can be differentiated from the streptococcic forms by its milder clinical characteristics, the absence of streptococci on repeated cultures and the absence of serologic evidence of infection therewith. In subsequent studies [52a] another mild infection called ARD (acute respiratory disease) was described and shown to be immunologically different from the common cold and from viral pneumonia. The infection is characterized by mild sore throat, but no mention is made as to whether or not it is the same as the exudative pharyngitis described by the same investigators.

In contrast with this form of pharyngitis, Rantz and his associates [53] studied an outbreak of hemolytic streptococcic sore throat. Clinical diagnosis was correct in 70 per cent of cases. The throat was painful,

50. Knight, C. A.: The Nucleic Acid and Carbohydrate of Influenza Virus, J. Exper. Med. **85**:99-115 (Jan.) 1947.

51. Reimann, H. A.: Viral Infections of the Respiratory Tract: Their Treatment and Prevention, J. A. M. A. **132**:487-493 (Nov. 2) 1946.

52. Exudative Tonsillitis and Pharyngitis of Unknown Cause, Commission on Respiratory Diseases, J. A. M. A. **133**:588-593 (March 1) 1947.

52a. The Commission on Acute Respiratory Diseases: Experimental Transmission of Minor Respiratory Illness to Human Volunteers by Filter-Passing Agents: I. Demonstration of Two Types of Illness Characterized by Long and Short Incubation Periods and Different Clinical Features, J. Clin. Investigation **26**:957-973 (Sept.) 1947; II. Immunity on Reinoculation with Agents from the Two Types of Minor Respiratory Illness and from Primary Atypical Pneumonia, ibid. **36**:974-982 (Sept.) 1947.

53. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic and Nonstreptococcic Diseases of Respiratory Tract: Comparative Clinical Study, Arch. Int. Med. **78**:369-386 (Oct.) 1946.

edematous and inflamed, with an exudate and swollen regional lymph nodes, as compared with nonstreptococcic infections in which the nasopharyngeal mucous membrane was nearly normal. However, according to observations made by the Army group and by my own group, inflammation, edema and exudate are present in both conditions but are less severe in the nonbacterial forms. Variations in severity of both forms make diagnosis in the individual case unreliable without cultural and serologic proof. No reference is made by either group to Adam's study,[54] in which the exudate in nonbacterial pharyngitis is composed chiefly of mononuclear cells in contrast with a polymorphonuclear exudate in streptococcic infection. The cellular reaction is of aid in diagnosis. Gannet and Deutsch in previous work found no immunity to colds after prophylactic injection of a dose of gamma globulin. In student volunteers given monthly injections of gamma globulin, Adams and Smith[55] seemed to show that infections of the respiratory tract occurred less often than in an equal-sized control group. No accidental serum hepatitis was observed.

According to a study by Sargent and his aides,[56] there appears to be an undefined constitutional or genetic factor which is operative in the etiology of the common cold.

Diagnosis.—In a paper pointing out clinical differential diagnostic difficulties in the group of infections of the respiratory tract encountered during epidemics of influenza Ziegler and his associates[57] depend more on laboratory tests for diagnosis. In a series of 26 patients some admitted as having viral pneumonia proved to have pneumococcic pneumonia and others had influenza. Because certain patients with influenza had pneumonia, they suspected the presence of two concurrent infections, influenza and viral pneumonia. It would seem more reasonable, however, to assume that the influenza virus alone caused the pneumonia. The authors rely heavily on the tests for agglutinin for streptococcus MG and for cold agglutination in the diagnosis of viral pneumonia, yet these reactions occur late in the disease in only half of the cases. In diagnosis, dependence should not be placed on the therapeutic response to sulfonamide drugs or penicillin.

Viral Pneumonias.—Besides a comprehensive review of the subject of viral pneumonia,[58] few papers have appeared during the year. Viral pneumonia, as now recognized, has apparently declined from almost

54. Adams, J. M.; Pennoyer, M. M., and Whiting, A. M.: Pathologic Study of the Acutely Inflamed Human Pharynx in Influenza Infection, Am. J. Dis. Child. **71**:162-170 (Feb.) 1946.

55. Adams, J. M., and Smith, N.: Clinical Trial of Gamma Globulin in the Prevention of Common Respiratory Diseases, Proc. Soc. Exper. Biol. & Med. **63**:446-449 (Nov.) 1946.

pandemic proportions in the years 1942 to 1944 to a few sporadic cases during the past winter consistent with the natural waxing and waning of epidemic diseases. In my experience it was outnumbered by cases of pneumococcic pneumonia, as in former years.

Adamson and Beamish,[59] in agreement with my own view, state that the term "atypical pneumonia" has resulted in much confusion in nomenclature of disease of the respiratory tract. They prefer to apply the term pneumonia only to pneumococcic pneumonia, other forms to be called pneumonitis. The term pneumonitis, they write, is a clinically descriptive one and should be used for these conditions: (1) common cold pneumonitis, (2) influenzal pneumonitis, (3) contamination pneumonitis, (4) exacerbation pneumonitis, (5) atelectatic pneumonitis, (6) allergic pneumonitis, (7) pneumonitis due to known viruses and rickettsias and (8) pneumonitis due to unknown viruses.

Eaton and his associates,[60] pursuing their previous lead, found increases of antibody titer for Eaton's AP (atypical pneumonia) virus in 62 per cent of 84 cases of viral pneumonia and in 19 per cent of 77 cases of undifferentiated infections of the respiratory tract without pneumonia. In only 35 per cent of patients with pneumonia and in only 2 per cent of those without pneumonia was agglutinin for streptococcus MG present. These results, according to the authors, aid in delineating another disease of the respiratory tract as an etiologic entity in line with influenza, both of which may occur in sporadic or epidemic form with or without pneumonia.

A surprising number of instances of pneumonia, clinically unsuspected and unrecognized, are brought to light by roentgenography in apparently normal persons. Stuart,[61] who studied 19,000 recruits, found evidence of "atypical pneumonia" in 42, or 0.2 per cent, each of whom were ambulant but had "colds."

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56. Sargent, F.; Lombard, O. M., and Sargent, V. W.: Further Studies on the Resistance to the Common Cold: The Importance of Constitution, Am. J. Hyg. **45**:29-32 (Jan.) 1947.

57. Ziegler, J. E., and others: Diagnosis of Acute Respiratory Tract Infections, Am. J. M. Sc. **213**:268-281 (March) 1947.

58. Reimann, H. A.: Viral Pneumonias and Pneumonias of Probable Viral Origin, Medicine **26**:167-219 (May) 1947.

59. Adamson, J. D., and Beamish, R. E.: Clinical Differentiation in the Syndrome Called Atypical Pneumonia, Canad. M. A. J. **56**:361-365 (April) 1947.

60. Eaton, M. D., and Van Herick, W.: Serological and Epidemiological Studies on Primary Atypical Pneumonia and Related Acute Upper Respiratory Disease, Am. J. Hyg. **45**:82-95 (Jan.) 1947.

61. Stuart, F. G.: Pathological Manifestations and Anatomical Variations in Pre-Enlistment Chest Roentgenograms, Canad. M. A. J. **52**:477-481 (May) 1945.

Kotin [62] observed 5 patients with severe viral pneumonia who apparently contracted the disease from a sixth member of the famliy. No other disease, mild or severe, occurred in equally exposed relatives or in the community at the time. Since all 6 patients were female and genetically related, a hereditary susceptibility to the infection is suggested. A genetic influence on susceptibility to the common cold was mentioned on a previous page.

Holmes reports [63] neurologic complications as acute polyneuritis, meningitis and encephalitis in patients with viral pneumonia.

The Pneumonia of Erythema Multiforme Exudativum.—By curious coincidence which occasionally occurs, four groups of observers report studies on pneumonia closely resembling viral pneumonia in cases of erythema multiforme exudativum.[64] It is characterized by a mononuclear cell exudate and is probably an integral part of the disease, presumably caused by a virus. The disease is a systemic one in which the lungs may be involved and is probably the same as Stevens-Johnson disease.[64c,d] It has been called dermatostomatitis and mucocutaneous fever, and it may be mistaken for Vincent's disease if fusospirochetal bacteria are present.

Psittacosis and Ornithosis.—Meyer and Eddie [65] report 2 more cases of psittacosis in which penicillin was therapeutically effective. Large amounts of penicillin, 320,000 units daily, are essential for success. They also report the existence of human carriers. Psittacosis virus was present in the pharyngeal secretions of 1 person for eight years. Contagiousness is apparently of a low order, since no other persons near these carriers contracted the infection.

Because of the presence of ornithosis in several species of birds thus far examined, it was predictable that others would be found. Studies by Pollard,[66] suggested by the presence of the disease in Fulmar petrels,

62. Kotin, E. H.: Probable Genetic Susceptibility to Viral Pneumonia, Ann. Int. Med., to be published.

63. Holmes, J. M.: Neurological Complications in Atypical Pneumonia, Brit. M. J. **1**:218-220 (Feb. 8) 1947.

64. (*a*) Stanyon, H. H., and Warner, W. P.: Mucosal Respiratory Syndrome, Canad. M. A. J. **53**:427-434 (Nov.) 1946. (*b*) Association of Pneumonia with Erythema Multiforme Exudativum, Commission on Acute Respiratory Disease, Arch. Int. Med. **78**:687-710 (Dec.) 1946. (*c*) Wentz, H. S., and Seiple, H. H.: Stevens-Johnson Syndrome: A Variation of Erythema Multiforme Exudativum (Hebra); Report of Two Cases, Ann. Int. Med. **26**:277-282 (Feb.) 1947. (*d*) Soll, S. N.: Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balanitis, Arch. Int. Med. **79**:475-500 (May) 1947.

65. Meyer, K. F., and Eddie, B.: The Knowledge of Human Virus Infections of Animal Origin, J. A. M. A. **133**:822-828 (March 22) 1947.

66. Pollard, M.: Ornithosis in Sea-Shore Birds, Proc. Soc. Exper. Biol. & Med. **64**:200-202 (Feb.) 1947.

revealed evidence of infection by the complement fixation test in 40 per cent of a variety of gulls, terns, pelicans and other shore birds. An ornithosis-like agent was isolated from birds of the willet species.

Vaporized triethylene glycol has a definite but limited value in sterilizing clouds of meningopneumonitis and psittacosis viruses suspended in the air of rooms.[67] Some of the virus escapes destruction, however, so that the method, while partly effective, is not wholly reliable. For epidemiologic control, it is better to stop the spread of infection by eliminating its source.

In a review [68] of the merits of various measures to control air-borne infection in general, it is recommended that the use of either ultraviolet rays or triethylene glycol aerosol must be supplemented by measures such as oiling to control dust in order to be effective. In several instances, aerosol treatment failed to reduce the incidence of air-borne infection. The committee does not recommend the general use of these disinfecting devices until further work has been done.

Pneumococcic Pneumonia.—In a series of papers in the September issue of the *American Journal of Hygiene,* Hodges and MacLeod describe epidemic pneumococcic pneumonia over a two and a half year period in a military camp. Pneumococcus type II predominated, but types 1, 5, 7, 12 and 14 all showed similar epidemiologic behavior. The person to person spread was greatest in classrooms, and the same incidence of the types of pneumococci was found in carriers as in the dust of rooms. The carrier rates were higher in winter, but in general they showed no close relation to the number of cases of pneumonia except those of types 4 and 12. Vaccination with specific polysaccharides reduced the carrier rate. There was no evidence to favor age, chilling or fatigue as important predisposing factors in causing pneumonia. One case of pneumonia occurred to every ten mild infections of the respiratory tract.

Wood and his associates [69] present evidence to show that phagocytosis of pneumococci may occur without the agency of a specific antibody or opsonin. Phagocytosis occurs in the pneumonic lung during sulfonamide therapy by direct action of phagocytes on the pneumococci. Direct phagocytosis probably also accounts for the rapid disposal of inhaled pathogenic bacteria. The authors believe, as others do, that

67. Rosebury, T.; Meikeljohn, G.; Kingsland, L. C., and Boldt, M. H.: Disinfection of Clouds of Meningopneumonitis and Psittacosis Viruses with Triethylene Glycol Vapor, J. Exper. Med. **85**:65-76 (Jan.) 1947.

68. Recent Studies on Disinfection of Air in Military Establishments, Committee on Sanitary Engineering, National Research Council, Am. J. Pub. Health **37**:189-198 (Feb.) 1947.

69. Wood, W. B.; Smith, M. R., and Watson, B.: Studies on the Mechanism of Recovery in Pneumococcal Pneumonia: IV. The Mechanism of Phagocytosis in the Absence of Antibody, J. Exper. Med. **84**:387-401 (Oct.) 1946.

the physical changes of the surface of bacteria is probably of great importance in phagocytosis. They imply that their "discovery" of surface phenomena clarifies certain problems in the recovery from infection but fail to mention previous studies of similar import by others. In studies published in 1932,[70] literature pertaining to the nonspecific relationship of fever and changes in blood protein to phagocytosis and recovery from infection was cited, and experiments were reported which showed that the increase of viscosity of the plasma was an important factor. Furthermore, phagocytosis is not the only important cause of recovery from pneumococcic pneumonia in particular or from infectious disease in general.

Coccidioidomycosis.—Forbus and Bestebreurtje[71] give a comprehensive review of the history of coccidioidomycosis and a discussion of the pathogenesis, clinical features, pathologic anatomy and other details in 95 cases of the severe generalized form as they occurred in the armed forces in the western states from 1941 to 1946. Of the 95 patients studied, 50 died. The disease primarily involves the lungs and in the majority of cases is mild. In a small proportion of patients infection persists and becomes disseminated at any time up to ten years. Of the 6,000 soldiers who were known to have had the disease in endemic areas and perhaps many who had subclinical infections, any are liable to later endogenous dissemination. The generalized form is granulomatous in nature and affects many organs and tissues. In patients who have had erythema nodosum in the early period the generalized form rarely develops. Person to person infection probably does not occur, and it is unlikely that the fungus can live if transplanted to other parts of the country. Contrary to previous views, the occurrence of pulmonary calcification which may be confused with that caused by tuberculosis and histoplasmosis was not observed in Forbus' group, but it may appear in patients who survive long enough. It had previously been reported after coccidioidomycosis by Aronson.

The infection is endemic in the southwestern area of the United States, in South America and in southern Europe. In patients infected in endemic areas the early or later form of disease may develop wherever they may be.

In another study,[72] 60 per cent of 1,350 persons discovered by the coccidioidin test to be infected were symptomless. Erythema nodosum

70. Reimann, H. A.: The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection, Ann. Int. Med. **6**:362-374 (Sept.) 1932.

71. Forbus, W., and Bestebreurtje, A. M.: Coccidioidomycosis: A Study of Ninety-Five Cases of the Disseminated Type with Special Reference to the Pathogenesis of the Disease, Mil. Surgeon **99**:653-719 (Nov.) 1946.

72. Smith, C. E.; Beard, R. R.; Whiting, E. G., and Rosenberger, H. C.: Varieties of Coccidioidal Infection in Relation to Epidemiology and Control of Diseases, Am. J. Pub. Health **36**:1394-1402 (Dec.) 1946.

occurred in 4.6 per cent. Dissemination occurred in only 1 per cent of white patients with clinically evident diseases, which amounts to 0.25 per cent for the total number of recognized infections. The incidence of dissemination is over ten times higher in Negroes.

Studies [73] in an army camp in the southwestern area of the United States confirm previous observations that dust is the chief mode of conveyance of infection. In such areas, grassing or oiling the surface helps to control the infection. Although the disease is generally believed not to be contagious, experiments show that it is possible to transmit infection from man to animal and from animal to animal by the intrabronchial inoculation of the spherules.[74]

Pulmonary Calcification from Histoplasmosis.—The frequency of pulmonary calcification, miliary or otherwise, as detected roentgenographically in persons in the central area of the United States in whom the reaction to the tuberculin skin test is negative has often given rise to controversy. Among 64 persons studied [75] calcification was not noted among any of those who reacted only to tuberculin, but 93 per cent of those with calcified areas showed reaction to histoplasmin alone and in 2 instances to both histoplasmin and tuberculin. The results suggest, as previous studies have, that pulmonary calcification in the central United States is most often caused by the agent of histoplasmosis, assuming that the test is a specific one.

Hemolytic Streptococcic Pharyngitis.—Rantz and his associates [76] made extensive studies of hemolytic streptococcic sore throat in soldiers, amplifying their previous reports. Streptococci of types 3, 17, 19, 30, 36 and 46 caused most of the attacks, and types 3, 17, 19 and 30 caused more severe disease with cutaneous rash than the others. The disease lasted only four days in 86 per cent of the cases. The severity was not related to the presence or absence of tonsils, to the severity of cervical adenitis or to the amount of exudate, but patients with an exanthem were sick longer. Therapy with sulfadiazine and penicillin, alone and in combination, had but slight effect on shortening the disease or in eradicating hemolytic streptococci from the nose and throat.

73. Smith, C. E.; Beard, R. R.; Rosenberger, H. G., and Whiting, E. G.: Effect of Season and Dust Control on Coccidioidomycosis, J. A. M. A. **132**:833-838 (Dec. 7) 1946.

74. Rosenthal, S. R., and Routien, J. B.: The Infectiousness of Coccidioidomycosis, Science **104**:479 (Nov. 22) 1946.

75. High, R. H.; Zwerling, H. B., and Furcolow, M. L.: Disseminated Pulmonary Calcification, Pub. Health Rep. **62**:20-29 (Jan. 3) 1947. Zwerling, H. B., and Palmer, C. E.: Pulmonary Calcification in Relation to Sensitivity to Histoplasmin, J. A. M. A. **134**:691-693 (June 21) 1947.

76. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Hemolytic Streptococcic Sore Throat: The Course of the Acute Disease, Arch. Int. Med. **79**:272-290 (March) 1947.

Persons who have mild or subclinical infections of the upper respiratory tract or those who have had "missed cases" caused by group A hemolytic streptococci may serve as carriers and disseminators of this germ, according to Lemon and Hamburger.[77] In an epidemiologic study in one season, "missed cases" probably comprised from 67 to 94 per cent of carriers. Mere "contact" carriers or those with no serologic evidence of infections were uncommon. Nasal carriers are more apt to transmit infection than those in whom the cocci are present only in the throat.

The reaction to the Dick test was positive in 28 per cent of soldiers who had acute infection of the respiratory tract.[78] The reaction was positive in both the viral type of disease and in that caused by hemolytic streptococci, which fact, the authors believe, indicates a lack of relationship between the reaction and specific immunity to infection with streptococci. The reaction to the Dick test is believed to become positive as a result of exposure to the bacteria and the development of acquired hypersensitivity to its products, but such a reaction does not necessarily indicate a natural susceptibility to the toxin.

In a study of the "poststreptococcic state",[79] certain patients who had recovered from an infection caused by hemolytic streptococci remained febrile for some time after; in others fever, arthritis, carditis, pneumonia, or lymphadenitis developed in early convalescence. Glomerulonephritis was not encountered. These apparent sequels were noted in 20 per cent of all cases of hemolytic streptococcic infection and could not be demonstrated to be the result of local extension of the initial process in the throat or the invasion of remote areas by the bacteria. In patients with arthritis and carditis the condition was indistinguishable from that of classic rheumatic fever. The pneumonia which was observed resembled viral pneumonia but for the presence of leukocytosis and a rapid sedimentation rate. The pneumonia presumably is akin to that which may accompany rheumatic fever but is milder. It is not caused primarily by the hemolytic streptococcus as a true streptococcic pneumonia.

The studies emphasize the seriousness of hemolytic streptococcic infections of the respiratory tract, especially since therapy with large amounts of sodium salicylate and a short course of penicillin with or

77. Lemon, H. M., and Hamburger, M.: Missed Cases and Contact Carriers Among Nasal Carriers of Beta Hemolytic Streptococci, J. Immunol. **54**:189-196 (Oct.) 1946.

78. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Dick Test in Military Personnel with Special Reference to Pathogenesis of Skin Reaction, New England J. Med. **235**:39-42 (July 11) 1946.

79. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat: The Poststreptococcic State, Arch. Int. Med. **79**:401-435 (April) 1947.

without a sulfonamide drug did not prevent these late nonsuppurative complications of unknown nature.

Diphtheria.—According to Anderson [80] there is no cause for alarm over the suspected appearance of a new highly virulent form of diphtheria bacilli as the cause of the great increase in severe diphtheria in Europe during the war. No new bacilli have been isolated. Diphtheria increased there because of the crowding, hardship, deprivation of food and poor medical care incident to the war. Immunization programs could not be carried out, but there is doubt as to the importance of the preventive role of this procedure, particularly among adults. Fanning, in this respect, reports [81] a severe outbreak of diphtheria in a school in which 94 per cent of the students had been previously immunized and 80 per cent were "Shick negative." The disease, therefore, may occur in a supposedly immunized community and may be severe in previously immunized persons, and the Shick test is not always reliable as an indicator of immunity.

In the United States and Canada diphtheria has increased in incidence since 1944, probably because of the natural epidemic behavior of the disease.

Although penicillin has no effect on the clinical course of diphtheria, it is said to reduce the duration of the convalescence and the carrier rate if given in doses of 120,000 or preferably 240,000 units daily for twelve days.[82]

Tuberculosis.—Tuberculosis as a cause of death could be eliminated within a generation by using the methods of control now at hand in a well coordinated attack.[83] The death rate already has been reduced by four fifths since 1900. Great progress has been made in the early detection of the disease and in the reduction of chances of becoming infected. The greatest problem at present rests in the control of tuberculosis among Negroes.

Similar views are given by Myers,[84] who outlines a program for control as adopted in Minneapolis. With a fundamental plan of proved effectiveness, the problem of tuberculosis could be solved. Roentgenograms made of each adult's lungs would detect active infections

80. Anderson, G. W.: Foreign and Domestic Trends in Diphtheria, Am. J. Pub. Health **37**:1-12 (Jan.) 1947.

81. Fanning, J.: Outbreak of Diphtheria in a Highly Immunized Community, Brit. M. J. **1**:371-372 (March 22) 1947.

82. Wienstein, L.: The Treatment of Acute Diphtheria and the Chronic Carrier State with Penicillin, Am. J. M. Sc. **213**:308-314 (March) 1947.

83. Wiping Out Tuberculosis in Our Time, Statist. Bull. Metrop. Life Insur. Co. **27**:1-3 (Nov.) 1946.

84. Myers, J. A.: The Establishment and Use of Fundamental Procedures in Tuberculosis Control, Pub. Health Rep. **61**:1563-1583 (Nov. 1) 1946.

responsible for the spread of the disease. Patients with such infections would be isolated and treated. The tuberculin test would serve to discover the remainder of persons with primary tuberculosis. In a decade after the use of this plan, the author predicts, the number of beds needed for tuberculous patients would be far less, and in another decade the disease could be suppressed to an irreducible minimum. The responsibility for these procedures lies with public health officials.

Hilleboe [85] calls attention to the controversial issues in the control of tuberculosis, as the diagnostic value of the tuberculin test, the accuracy of roentgenologic interpretation and the value of vaccination with BCG.

At a recent conference [86] the use of BCG vaccine was discussed. Vaccination, all agree, is harmless; it confers increased resistance to tuberculosis and converts a large percentage of nonreactors to tuberculin into reactors. But since information about the degree and duration of the immunity given by the vaccine is incomplete, BCG should not be made available commercially at present. According to a report from Norway,[87] BCG vaccine gives protection against tuberculosis in 75 to 95 per cent of subjects. According to Birkhaug,[87a] Scandinavian physicians regard BCG vaccine as the best measure of controlling tuberculosis in young adults.

The use of streptomycin for tuberculosis has been discussed.

RHEUMATIC FEVER

Rheumatic fever often manifests itself in deceptive forms.[88] It may be encountered with no articular symptoms, as a monarticular involvement or as arthritis of the hands or feet, with prodromal aching for days to weeks before the typical symptoms appear; there may be no fever during the acute stage, and it may begin with pericarditis or pneumonia.

Two other groups of observers like Rantz, as discussed in a preceding section, comment on our inadequate knowledge of "rheumatic pneumonia." One group [89] did not encounter mild, fleeting pulmonary lesions as described by Rantz [79] in the poststreptococcic state. Instead, all 6

85. Hilleboe, H. E.: Controversial Issues in Tuberculosis Control, Pub. Health Rep. **61**:1561-1563 (Nov. 1) 1946.

86. Report of a Conference on BCG Vaccination, Pub. Health Rep. **62**:346-350 (March 7) 1947.

87. Hertzberg, G.: Recent Experience with BCG Vaccination in Norway, Tubercle **28**:1-10 (Jan.) 1947.

87a. Birkhaug, K.: BCG Vaccination in Scandinavia: Twenty Years of Uninterrupted Vaccination Against Tuberculosis, Am. Rev. Tuberc. **55**:234-249 (March) 1947.

88. Sokolow, M., and Snell, A. M.: Atypical Features of Rheumatic Fever in Young Adults, J. A. M. A. **133**:981-989 (April 5) 1947.

patients described died, a fact which indicates the serious import of rheumatic pneumonia. The condition occurs far oftener in rheumatic fever than other forms of pneumonia and can be recognized relatively easily. Both Seldin [89] and Mossberger,[90] like Rantz, point out certain resemblances to viral pneumonia, but rheumatic pneumonia almost certainly consists of the specific reaction of the lung during rheumatic fever.

According to Bruetsch [91] the brain may be involved in the rheumatic state. He reports rheumatic vascular obliterations in the smaller meningeal and cortical branches of the cerebral vessels which can be found only by making serial sections. While there is little doubt that the cerebral vessels may be involved as well as other vessels in the body, one may question the author's view, as skeptical discussers of his paper have, incriminating rheumatic disease as an important cause of mental disease. Breutsch reports histologic evidence of rheumatic brain disease in 9 per cent of patients with schizophrenia. According to some of the discussers the lesions are nonspecific and are found in other conditions as well.

In testing Guerra's theory that the symptoms of rheumatic fever are influenced favorably after the inhibition of hyaluronidase by sodium salicylate, Pike [92] was unable to show that the drug had any inhibiting effects on streptococcic hyaluronidase in vitro. Others,[93] however, show that sodium salicylate does inhibit the spreading effect of hyaluronidase in the animal body. Greater amounts of salicylate are needed to accomplish the effect in the test tube. An inhibiting substance able to neutralize an enzyme (hyaluronidase) made by hemolytic streptococci was demonstrated in the blood of many persons but particularly in those with rheumatic fever.[94] The matter obviously needs further study.

Other studies [94a] which deal with the pathogenesis of rheumatic fever involve hyaluronic acid in so-called albumin-bacterioplasma con-

89. Seldin, D. W.; Kaplan, H. S., and Bunting, H.: Rheumatic Pneumonia, Ann. Int. Med. **26**:496-520 (April) 1947.

90. Mossberger, J. I.: Rheumatic Pneumonia: Report of Two Cases, J. Pediat. **30**:113-122 (Feb.) 1947.

91. Bruetsch, W. L.: Rheumatic Brain Disease, J. A. M. A. **134**:450-453 (May 31) 1947.

92. Pike, R. M.: Failure of Sodium Salicylate to Inhibit Hyaluronidase in Vitro, Science **105**:391 (April 11) 1947.

93. Dorfman, A.; Reimers, E. J., and Ott, M. L.: Action of Sodium Salicylate on Hyaluronidase, Proc. Soc. Exper. Biol. & Med. **64**:357-360 (March) 1947.

94. Friere, G. J., and Wenner, H. A.: On the Occurrence in Human Serum of an Inhibitory Substance to Hyaluronidase Produced by a Strain of Hemolytic Streptococcus, J. Infect. Dis. **80**:185-193 (March-April) 1947.

94a. Schultz, M. P., and Rose, E. J.: Albumin-Bacterioplasma Conjugates with Special Reference to the Etiology of Rheumatic Fever, Pub. Health Rep. **62**:1009-1022 (July 11) 1947.

jugates. Apparently, extracts of embryonal connective tissue and human serum combine in some way with the products of hemolytic streptococci to form toxic substances. These substances cause cardiac lesions akin to those of rheumatic fever when injected into animals. They cause pain at the site of injection, systemic disturbance suggestive of extensive injury to tissue and occasionally the major manifestation of the disease in patients convalescent from rheumatic fever and systemic reactions of fever and increased number of leukocytes in nonrheumatic control persons. What seems to be of especial significance is that after gradually increasing doses the development of tolerance or of increased resistance was noted both in rheumatic and in control persons.

According to Harris' observations,[95] massive doses of salicylates, once recommended for the treatment of acute rheumatic fever, do not suppress the inflammatory process.

Dry, Butt and Scheifley [96] comment on the influence of paraaminobenzoic acid on diverse biologic activities, including its antisulfonamide action, its inhibiting effect on growth of rickettsia and its growth-promoting effects. In their experiments paraaminobenzoic acid when given with sodium salicylate during the course of therapy of rheumatic fever greatly raised the level of salicylate in the blood. Paraaminobenzoic acid apparently was therapeutically effective in lowering the fever and lessening the arthralgia in a few cases of rheumatic fever.[96a]

Burke [97] gave three pastilles of 500 units of penicillin daily for a year to 10 rheumatic patients and compared their course with that of 10 untreated patients. Rheumatic manifestations during this period were six times more frequent in the control group, suggesting the value of penicillin as a prophylactic agent. It may be recalled that similar reports were published several years ago about prophylaxis with sulfonamide compounds.

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95. Harris, T. N.: The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever, Am. J. M. Sc. **213**:428-487 (April) 1947.

96. Dry, T. J.; Butt, H. R., and Scheifley, C. H.: The Effect of Oral Administration of Para-Aminobenzoic Acid on the Concentration of Salicylates in the Blood: Preliminary Report, Proc. Staff Meet., Mayo Clin. **21**:497-504 (Dec. 24) 1946.

96a. Rosenblum, H., and Fraser, L. E.: Effect of Para-Aminobenzoic Acid on Fever and Joint Pains of Acute Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **65**:178-180 (June) 1947.

97. Burke, P. J.: Penicillin Prophylaxis in Acute Rheumatism, Lancet **1**:255-256 (Feb. 15) 1947.

Rheumatoid Arthritis.—In a series of papers, Wallis [98] concludes that rheumatoid arthritis is not proved to be of bacterial origin, especially as regards hemolytic streptococci. The serologic reactions which have thus far been studied and thought to be of aid in signifying certain causative agents are of doubtful value and probably represent the nonspecific enhancement of normally present antibodies. By electromyographic studies,[98a] further evidence accrues of an involvement of the neuromuscular system to account for certain neurologic symptoms and signs characteristic of rheumatoid arthritis and probably partly explains its pathogenesis. There may also be lesions of the lower motor neurons, as in certain other diseases. Histologic changes were found in the lateral projections of the anterior horns of the cord.

ENTERIC DISEASES

Shigellosis, or Bacillary Dysentery.—Attempts were made to infect volunteers with dysentery bacilli.[99] There was no constant relation between invasiveness of the bacteria in experimental animals and that in man. Strains virulent for animals were not always infective in man, and the opposite was noted. Relatively large doses of ten billion bacilli of the Flexner W strain caused only slight cramps in 1 volunteer and in 3 others caused nausea, headache, chills and diarrhea. None had fever, and in 1 symptoms lasted ten days. In one experiment a dose of fifty billion bacilli caused only mild headache, anorexia and slight cramps. Other strains of the Flexner type of bacilli caused symptoms typical of dysentery twelve hours after ingestion in about half of the subjects, and in many no symptoms at all developed. Obviously, other factors besides the presence of bacilli alone are needed before disease occurs. In most successful infections the "incubation" period was less than twenty-four hours, diarrhea appearing eighteen to twenty-four hours after ingestion of the inoculum. Nausea and vomiting, the chief early symptoms in the volunteers, when encountered in naturally infected persons would hardly lead to a suspicion or a diagnosis of shigellosis and certainly not of "dysentery."

98. Wallis, A. D.: Rheumatoid Arthritis: I. Introduction to a Study of Its Pathogenesis, Am. J. M. Sc. **212**:713-715 (Dec.) 1946; II. Non-Specific Serologic Reactions, ibid. **212**:716-717 (Dec.) 1946; III. The Pneumococcus Antibodies, ibid. **212**:718-722 (Dec.) 1946; IV. Hemolytic Streptococcus Precipitin Reactions, ibid. **213**:87-93 (Jan.) 1947; V. The Agglutination of Hemolytic Streptococci, ibid. **213**:94-96 (Jan.) 1947.

98a. Morrison, L. R., and others: The Neuromuscular System in Rheumatoid Arthritis: Electromyographic and Histologic Observations, Am. J. M. Sc. **214**: 33-49 (July) 1947.

99. Shaughnessy, H. J.; Olsson, R. C.; Bass, K.; Friewer, F., and Levinson, S. O.: Experimental Human Dysentery: Polyvalent Dysentery Vaccine in Its Prevention, J. A. M. A. **132**:362-368 (Oct. 19) 1946.

There was no evidence of the value of vaccine prepared with either heat-killed or irradiated bacilli in the prevention of experimentally induced shigellosis. Attacks of dysentery and the carrier state were easily controlled with sulfadiazine. Interest in the presence of antibody against dysentery bacilli in the stools of patients with dysentery, begun in 1922, was revived by the studies of Burrows, as yet unpublished, and by those of Harrison and Banvard.[99a] The coproantibody, as it is called, was found to be present as early as the third day of disease, to increase in titer up to about the ninth day and then to disappear rapidly. The development of agglutinin within three days is remarkably soon for any disease. This is in contrast with antibody in the blood, which does not appear as a rule before recovery is established and which persists for many weeks. The presence of specific antidysentery bacillus fecal agglutinin in 97 per cent of patients suggests that their demonstration is a valuable diagnostic aid. The existence of coproantibody may also explain certain puzzling phases of immunity against cholera, bacillary dysentery and salmonella enteritis and may serve as a mechanism which aids in recovery from enteric infections.

The old controversy about the relationship of bacillary dysentery to chronic ulcerative colitis again arises. In Felsen and Wolarsky's follow-up study[100] of an epidemic of bacillary dysentery in 1934, 10.7 per cent of victims were found to have had ulcerative colitis or ileitis nine to twelve months later. A new study was prompted by the great number of attacks of dysentery in military personnel during the war. In one group of 61 patients with ulcerative colitis studied five to thirty-one months after an acute attack of dysentery, most of them showed inflammation of the bowel wall, and dysentery bacilli were recovered from 10 per cent. The authors believe that chronic ulcerative colitis and ileitis are the result of acute bacillary dysentery. While no one doubts that shigellosis may lead to chronic colitis in a small percentage of patients, one can hardly agree that bacillary dysentery is the cause of most cases of nonspecific ulcerative colitis.

Study was made of several epidemics of gastroenteritis on ships during the war.[101] They were caused in about equal numbers by Shigella, Salmonella and unknown agents, probably viruses (viral dysentery). Staphylococci may have been operative in some of the milder outbreaks but were not established as a cause. Of the Shigella group,

99a. Harrison, P. E., and Banvard, J.: Coproantibody Excretion During Enteric Infections, Science **106**:189 (Aug. 29) 1947.

100. Felsen, J., and Wolarsky, W.: Bacillary Dysentery and Chronic Ulcerative Colitis in World War II, Science **105**:213 (Feb. 21) 1947.

101. Meyers, W. A.: Gastroenteritis Aboard Ship: Common Types Encountered and the Prevention and Control of Outbreaks, Pub. Health Rep. **61**:1853-1858 (Dec. 20) 1946.

Shigella flexneri III was the commonest type. The chief sources of infection were food handled by carriers on board ship, contaminated food eaten ashore, convalescent carriers on board and the domestic use of contaminated sea water. Salmonella infections were usually milder than shigellosis and came from the meat of turkeys, chickens and salmon. Measures for the prevention and management of outbreaks on shipboard are outlined.

A progress report of advances in knowledge of dysentery and its causative bacilli gained between 1942 and 1946 was published.[102] Particular attention is given to the confused problem of classification. Dysentery and diarrhea exceeded malaria as the most common "tropical" disease in our armed forces between 1942 and 1945.[103]

Viral Dysentery.—English physicians describe[104] coincident epidemics of Sonne bacillary dysentery and nonspecific gastroenteritis among nurses. The former was explosive in nature, and in the latter the cases were distributed over several months as previously described in other epidemics of "viral dysentery." Clinically the two diseases were indistinguishable. Bacillary dysentery was controlled with sulfaguanidine; viral dysentery was not. The authors agree that a virus is the most probable cause of the nonspecific gastroenteritis. One may object to the suffix "itis" implying inflammation, since fever is often absent, the stools do not contain blood or pus and the leukocyte count is normal.

Other British physicians[104a] describe an outbreak in which both infants and adults were sick.

Typhoid.—In Stuart and Pullen's analysis[105] of 360 cases of typhoid, in only 40 per cent had the disease been correctly diagnosed when the patients entered the hospital. Symptoms referable to the respiratory tract most often were confusing since 87 per cent of patients had coryza, 86 per cent coughed, 84 per cent had sore throat, rales were heard in 64 per cent and 12 per cent had pneumonia. The mortality rate was 13 per cent. Sulfonamide therapy was of no value.

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102. Weil, A. J.: Dysentery: A Progress Report for the Years 1942 to 1946, J. Immunol. **55**:363-405 (April) 1947.

103. Sapero, J. J.: Tropical Diseases in Veterans of World War II, New England J. Med. **235**:843-836 (Dec. 12) 1946.

104. Martin, L., and Wilson, M. M: Sonne Dysentery and Non-Specific Gastro-Enteritis in a Hospital, Lancet **1**:553-555 (April 26) 1947.

104a. Cook, G. T., and Marmion, B. P.: Gastroenteritis of Unknown Etiology: An Outbreak in a Maternity Unit, Brit. M. J. **2**:446-450 (Sept. 20) 1947.

105. Stuart, B. M., and Pullen, R. L.: Typhoid: Clinical Analysis of Three Hundred and Sixty Cases, Arch. Int. Med **78**:629-661 (Dec) 1946.

Perforation of the ileum in typhoid was given special study by Dunkerly.[106] The incident occurred in 1 per cent of 1,077 patients, some of them ambulatory. The mortality rate was 55 per cent in patients operated on. He recommends a full diet to prevent the accident.

A case of typhoid osteomyelitis of the skull which developed twenty-five years after an attack of typhoid is reported.[106a] A pure culture of nonviable forms was derived from the lesion, but no typhoid bacilli were present in the bile or the stools, and the reaction to the Widal test was negative. Streptomycin, tyrocidin, gramicidin and acriflavine applied locally and penicillin with a sulfonamide drug and antityphoid vaccination had no influence on the infection.

The residual fraction or supposed impurities of streptomycin were found to be two to five times more effective against Eberthella typhosa than purified streptomycin.[106b]

Cholera.—Although Reimann and his associates[107] were not impressed by the effects of sulfadiazine on cholera, Chu and others,[108] observing the same group of patients in Chungking, felt that the disease was shortened significantly by chemotherapy, as did Chu and Huang concerning other patients in Foochow.

In extensive studies on the bacteriology of cholera Burrows and his associates[109] point out how uncertain is the value of specific vaccination and conclude that previous experience indicates the development of only a low grade of immunity after vaccination. They discuss the difficulties of classifying vibrios, the uncertainty in differentiation on the basis of their chemical constituents and the report that no instance of a chronic carrier of the classic cholera vibrio has been discovered. El Tor vibrios, however, are found in carriers and do cause cholera-like

106. Dunkerly, G. E.: Perforation of the Ileum in Enteric Fever, Brit. M. J. **2**:454-457 (Sept. 28) 1946

106a. Haven, H.: Typhoid Osteomyelitis of the Skull, Bull. Mason Clin. **1**: 55-59 (June) 1947.

106b. Hobby, G. L., and Lenert, T. F.: Biological Activity of a Residual Form of Streptomycin Against Eberthella Typhosa, Proc. Soc. Exper. Biol. & Med. **65**:249-254 (June) 1947.

107. Reimann, H. A., and others: Asiatic Cholera: Clinical Study and Experimental Therapy with Streptomycin, Am. J. Trop. Med. **26**:631-647 (Sept.) 1946.

108. Chu, L. W., and Huang, C. H.: Effect of Sulfadiazine on Cholera, Am. J. Trop Med. **26**:821-823 (Nov.) 1946. Chu, L. W.; Huang, C. H.; Chang, C. T., and Kao, H. C.: Sulfonamide Drugs in the Treatment of Cholera, ibid. **26**:825-830 (Nov.) 1946.

109. Burrows, W.; Mather, A. N.; Elliott, M. E., and Wagner, S. M.: Studies on the Immunity to Asiatic Cholera: I. Introduction, J. Infect. Dis. **79**:159-167 (Sept.-Oct.) 1946. Burrows, W.; Mather, A. M.; McGann, V. G., and Wagner, S. M.: Studies on the Immunity to Asiatic Cholera: II. The O and H Antigenic Structure of the Cholera and Related Vibrios, ibid. **79**:168-197 (Sept.-Oct.) 1946.

disease. It was suggested elsewhere that perhaps vibrios exist in carriers in an unrecognizable variant form. They propose a new classification for Vibrios comma, as follows: type A, AB, AC and ABC, dependent on a combination of type-specific antigens, the letters to replace the Japanese eponyms in current use. Type A is a newly recognized specific form. By using this method of classification, Burrows identified nine strains of V. comma obtained by Reimann [110] from cholera patients, as follows: three were of type AB (Ogawa type), two were type AC (Inaba), two were type ABC (Hikojima) and two contained antigen B but lacked antigen A. The last two, according to Burrows, are not true cholera vibrios. It was somewhat surprising to find so many varieties of V. comma in patients in a local community. The question arises of whether one variety initiates an outbreak and other types arise later by type transformation or as variant forms or whether various types are always present and cause simultaneous infections in an epidemic.

Thousands of cases of cholera were reported from Korea, China and India in 1946.[111] An epidemic occurred in Egypt in the autumn of 1947.

OTHER BACILLARY DISEASES

Chronic Brucellosis.—Evans reviews [112] the history of the development of knowledge of brucellosis in this country beginning with Craig's recognition of the first case in 1906. She estimates the existence at present of 40,000 cases of acute or chronic brucellosis in the United States. Perhaps 4,000,000 persons are infected annually, but only a small percentage become sick enough to seek medical aid.

According to Darley and Gordon,[113] the intradermal test is the reaction most consistently positive in chronic brucellosis, but it does not distinguish past from existing infection. In applying the test to a large number of patients with obscure conditions, they were unable to find brucellosis as an important cause of allergic disturbances, chronic arthritis or psychoneurosis. The most frequent symptoms in 74 patients with chronic brucellosis were fatigue, generalized aches and pains, headache, digestive disturbance and low grade fever. Positive agglutination reaction occurred in many of these patients. One can hardly agree with

110. Reimann, H. A.: Further Note on the Classification of Vibrios from the 1945 Cholera Epidemic in Chungking, Am. J. Trop. Med. **27**:503 (July) 1947.

111. Foreign Reports, Pub. Health Rep. **62**:622 (April 25) 1947.

112. Evans, A. C.: Brucellosis in the United States, Pub. Health Rep. **37**:139-151 (Feb) 1947.

113. Darley, W., and Gordon, R. W.: Brucella Sensitization: A Clinical Evaluation, Ann. Int. Med. **26**:528-541 (April) 1947.

the authors, however, that chronic brucellosis is a separate clinical entity. It is the chronic form of brucellosis.

Sulfadiazine, penicillin and streptomycin were ineffective in the treatment of patients who acquired brucellosis as accidental laboratory infections.[5]

Glanders.—Six cases of glanders contracted as laboratory infections are reported,[114] but the clinical descriptions of them are so different from that of glanders in medical textbooks that several questions arise. No discussion or explanation of this divergence is given, nor was the discrepancy noted editorially.[115] Either the books are wrong or they fail to describe the mildest forms, which may be contracted by inhalation of floating bacilli instead of by natural contact infection, or the cases reported were not of glanders. Six persons working with cultures of Malleomyces mallei became sick with evidence of pulmonary involvement. The authors report striking persistent leukopenia and relative lymphocytosis as a characteristic feature, yet the lowest count mentioned was 5,000 and the highest lymphocyte percentage 45. In almost all cases the normal count was undisturbed; one count was 10,000 and one 18,000. Diagnosis was based on the known exposure to infection, on the reaction to the skin test and on the agglutinin titer and the fixation of the complement. In no case were glanders bacilli recovered. The question may be raised of whether exposure alone to the bacilli may have caused some of these reactions to become positive. The condition may have been confused with viral pneumonia or malaria or, in 1 case, with brucellosis which had occurred previously. Curiously, sulfonamide therapy was begun in most cases after recovery seemed to be established.

Melioidosis.—The first indigenous case of melioidosis in the United States was discovered in St. Louis.[116] The patient had the chronic form, with ulcers and sinuses on the thigh for eight years, during which time nearly eighty operations had been performed for drainage. Various sulfonamide compounds, penicillin and streptomycin were ineffective in therapy. Widespread cautery excision and skin grafting have given the best result to date.

Tularemia.—Jackson [117] advocates the treatment of tularemia with bismuth sodium tartrate as preferable to streptomycin. It is cheaper, easier to give and according to his results is more efficient in rapid cure than streptomycin. No details are given in the paper, and the

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114. Howe, C., and Miller, W. R.: Human Glanders: Report of Six Cases, Ann. Int. Med. **26**:93-115 (Jan.) 1947.

115. Human Glanders, editorial, J. A. M. A. **133**:622 (March 1) 1947.

116. McDowell, F., and Varney, P. L.: Melioidosis: Report of First Case from the Western Hemisphere, J. A. M. A. **134**:361-362 (May 24) 1947.

117. Jackson, W. W.: Further Report on the Use of Bismuth Sodium Tartrate Intravenously in the Treatment of Two Hundred and Three Additional Patients with Tularemia, Am. J. M. Sc. **213**:358-361 (March) 1947.

work needs confirmation or rejection. Tularemia was observed in Austria and in France.[117a]

Plague.—The mortality rate of plague during an epidemic in Foochow was 51 per cent up to July 18, 1944.[118] Among 25 patients admitted after July 18 who were treated with sulfadiazine the rate was 20 per cent. Sulfadiazine is said to be the drug of choice.

In a personal communication one of the authors, Dr. L. W. Chu, reports the successful treatment of a patient with pneumonic plague with streptomycin. The infection was contracted in a laboratory. The same author, with Huang, reports excellent effects in the treatment of bubonic plague with sulfadiazine. Bacilli, however, often survive in the bubos. Plague was successfully treated with streptomycin in Argentina.[118a]

In Africa treatment with sulfathiazole given intramuscularly and sulfadiazine given intravenously gave a mortality rate of only 6.6 per cent in patients treated early.[119] In patients treated twenty-four hours or more after the onset of illness the rate was 19.7 per cent. No control patients were used for comparison. All 19 patients with nonbubonic plague died. Grasset reports[120] success in immunization against plague with living avirulent plague bacilli. No ill effects are recorded.

Eight cases of plague with meningitis were studied[121] among 203 cases of plague in China in 1943 to 1945. One patient had the rare form of primary plague meningitis.

An epidemic of plague occurred in Africa in 1944-1945.[122] Thousands of cases of plague were reported from Southeast Asia in 1946 and several hundred from South America.[111] Outbreaks occurred in Turkey and in Palestine in the spring and summer of 1947.[122a]

117a. Puntigam, F.: Epidemiology of Tularemia in Lower Austria, Wien. klin. Wchnschr. **59**:103-105 (Feb. 21) 1947. First Cases of Tularemia in France, Foreign Letters, J. A. M. A. **135**:176 (Sept. 20) 1947.

118. Huang, C. H., and Chu, L. W.: Treatment of Bubonic Plague with Sulfadiazine, Am. J. Trop. Med. **26**:831-839 (Nov.) 1946.

118a. Videla, C. A.: Clinical Course and Treatment of Bubonic Plague, Rev. Assoc. Med. argent. **61**:15-20 (Jan.-Feb.) 1947.

119. Simeons, A. T. W., and Chhatre, K. D.: One Thousand Cases of Bubonic Plague Treated in an Emergency Plague Hospital, Indian M. Gaz. **81**:235-246 (June-July) 1946.

120. Grasset, E.: Control of Plague by Means of Live Avirulent Plague Vaccine in Southern Africa (1941-1944), Tr. Roy. Soc. Trop. Med. & Hyg. **40**:275-294 (Dec.) 1946.

121. Landsborough, D., and Tunnell, N.: Observations on Plague Meningitis, Brit. M. J. **1**:4-7 (Jan. 4) 1047.

122. Davis, D. H. S.: Plague Survey of Ngamiland, Bechuanaland Protectorate During Epidemic of 1944-1945, South African M. J. **20**:462-466 (Aug. 24) 1946.

122a. Outbreak of Bubonic Plague, Foreign Letters, J. A. M. A. **134**:1040 (July 19) 1947. Bubonic Plague in Haifa, Medical News, ibid. **134**:1035 (July 19) 1947.

Wayson [123] resurrects the controversy as to whether (*a*) plague among the rodents of this country is "spreading" eastward or whether (*b*) investigations to detect plague are spreading eastward. On the first assumption, plague has "spread" to South America since it was recently discovered in ground squirrels of Peru,[124] but, in keeping with the second assumption, investigators discovered sylvatic plague there, just as it was discovered when sought in the United States and in Africa. It is likely that plague was always present wherever certain rodents are found and is not necessarily spreading. It has not been reported east of Minnesota or Kansas,[124a] where there are no colonizing squirrels and prairie dogs which are reservoirs of infection.

According to Wayson plague is perpetuated from year to year in infected fleas which survive the winter. He found no evidence that rodent carriers of infection are factors in enzootic plague, although both hibernating and nonhibernating animals occasionally are found to be infected.

Leprosy.—Faget [125] points out that leprosy is being introduced constantly into the western states by oriental and Mexican immigrants but that a few indigenous cases occur. The most active focus is found in the Gulf Coast States. It is communicable in Texas, where most of 226 patients from that state were infected. Leprosy was brought to Florida before 1776 by African slaves.

Leprosy is of greatest menace to members of a household containing a patient. Patients prefer the euphemism "Hansen's disease" to the term leprosy. "Promin" (sodium p,p′-diaminodiphenylsulfone-n,n′-didextrose sulfonate) is replacing chaulmoogra oil in therapy.

Scleroma and Rhinoscleroma.—There is doubt as to whether the bacterium Klebsiella rhinoscleromatis, which resembles Friedländer bacilli, is the cause of this disease. In new studies [126] it was again isolated from 6 patients who were genetically related members of a family, and the complement fixation test suggested its etiologic relation.[127] It is uncertain if scleroma is a hereditary condition causing lesions inhabited by the bacillus in question as a saprophyte or if, as in leprosy, members

123. Wayson, N. E.: Plague: Field Studies in Western United States During Ten Years (1936-1945), Pub. Health Rep. **62**:780-791 (May 30) 1947.

124. Macchiavello, A.: Sylvatic Plague Found in Peru, Medical News, J. A. M. A. **133**:957 (March 29) 1947.

124a. Plague Infection Reported in the United States in 1946, Pub. Health Rep. **62**:1336 (Sept. 12) 1947.

125. Faget, G. H.: The Story of the National Leprosarium, Pub. Health Rep. **61**:1871-1883 (Dec. 27) 1946.

126. Levine, M. G.; Hoyt, R. E., and Paterson, J. E.: Scleroma: An Etiological Study, J. Clin. Investigation **26**:281-286 (March) 1947.

127. Levine, M. G., and Hoyt, R. E.: Scleroma: Complement Fixation Test, Proc. Soc. Exper. Biol. & Med. **65**:70-72 (May) 1947.

of a family are infected by continued close contact with a victim of the disease.

VIRAL DISEASES

Poliomyelitis.—According to Bodian and Howe [128] there is no final proof of the route followed by the poliomyelitis virus from the portal of entry to the central nervous system of man. If passage by way of the olfactory system and the bloodstream is excluded, the most likely pathways are through the fifth, seventh and ninth cranial nerves, which serve the oropharynx, and the tenth, which controls the lower intestinal tract. Mucous membranes in the areas mentioned are the only ones regularly shown to contain the virus in man. Ward and Walters [129] demonstrated the virus of poliomyelitis in secretions expelled from the mouth and nose in 2 of 19 patients in the early period of the disease. The virus, therefore, probably escapes from these areas under natural conditions to transmit disease to persons who are in the proximity of the patient. Blow flies (Phormia regina) were artificially infected with the virus of human poliomyelitis.[129a] Virus persisted in their excreta for three weeks.

Melnick and Horstmann [130] confirm Bodian's studies on the suitability of chimpanzees for study of the problem of immunity because they react like man to infection. Chimpanzees infected by ingesting the virus become symptomless carriers or have subclinical infection which evokes immunity. Chimpanzees so infected were subsequently resistant to reinfection with the same virus but not to reinfection with different ones. Howe and Bodian [131] found poliomyelitis virus in the throats of 2 healthy children, in both of whom antibody against the virus had developed one year later. These experiments and observations tend to confirm the general impression that human beings may be infected without showing clinical evidence of disease and thus become immune to reinfection with the same type of virus. The authors suggest the use of prophylactic vaccine subject to the same restrictions of specificity that limit the value of vaccines for influenza.

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128. Bodian, D., and Howe, H. A.: The Significance of Lesions in Peripheral Ganglia in Chimpanzee and in Human Poliomyelitis, J. Exper. Med. **85**:231-241 (March) 1947.

129. Ward, R., and Walters, B.: Elimination of Poliomyelitis Virus from Human Mouth or Nose, Bull. Johns Hopkins Hosp. **80**:98-106 (Jan.) 1947.

129a. Melnick, J. L., and Penner, L. R.: Experimental Infection of Flies with Human Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **65**:342-346 (June) 1947.

130. Melnick, J. L., and Horstmann, D. M.: Active Immunity to Poliomyelitis in Chimpanzees Following Subclinical Infection, J. Exper. Med. **85**:287-303 (March) 1947.

131. Howe, H. A., and Bodian, D.: Isolation of Poliomyelitis Virus from the Throats of Symptomless Children, Am. J. Hyg. **45**:219-222 (March) 1947.

Another fatal case of poliomyelitis in which the infection was apparently contracted in a laboratory was reported.[132] As calculated, the probable attack rate among laboratory workers who handle poliomyelitis viruses or are exposed to them is 2 in 50 to 75. This is much higher than the attack rate in natural epidemics. Contact with freshly isolated strains is especially dangerous. In the case described infecton apparently occurred through an injury to the skin of the arm, since virus was isolated from the lymph nodes draining the area and not from others.

Poliomyelitis virus is inactivated in the stomach at the hydrogen ion concentration which exists when only gastric juice is present and at the height of the digestive process.[133] When the acidity lessens, the virus passes through the stomach unharmed.

By a new method of inoculation with autolyzed brain tissue as an adjuvant, Milzer and Byrd[134] transmitted poliomyelitis virus directly from human feces and spinal cord to white mice. The virus may also be transmitted in this manner to other varieties of mice, to hamsters and to rhesus monkeys. The technic, if successful, will greatly simplify laboratory procedure for diagnosis, but according to reports other workers are having difficulty in repeating the method.

Poliomyelitis was thought to be uncommon in the tropics,[135] but as in the case of other supposedly uncommon conditions it is present and can be found if sought. Outbreaks are now recorded from many primitive areas.[136]

Smallpox.—Thousands of cases of smallpox were reported from Asia and Africa in 1946.[137] During early spring, 8 cases occurred in New York city and a few others elsewhere, evidently traced to a traveler who caught the disease in Mexico. The outbreak caused great alarm, emphasized the danger of an explosive outbreak in persons who are not immune and led to the prompt vaccination of thousands of persons. There is considerable doubt if the duration of protection after vaccination lasts much more than six months.

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132. Wenner, H. A., and Paul, J. H.: Fatal Infection with Poliomyelitis Virus in a Laboratory Technician: Isolation of Virus from Lymph Nodes, Am. J. M. Sc. **213**:9-18 (Jan.) 1947.

133. Faber, H. K., and Dong, L.: Inactivation of Poliomyelitis Virus in Relation to Gastric and Intestinal Digestion, Proc. Soc. Exper. Biol. & Med. **63**:575-578 (Dec.) 1946.

134. Milzer, A., and Byrd, C. L.: Autolyzed Brain Tissue as a Means of Facilitating Transfer of Experimental Poliomyelitis, Science **105**:70-72 (Jan. 17) 1947.

135. Sabin, A. B.: The Epidemiology of Poliomyelitis: Problems at Home and Among the Armed Forces Abroad, J. A. M. A. **134**:749-756 (June 28) 1947.

136. Dauer, C. C.: Incidence of Poliomyelitis in 1946, Pub. Health Rep. **62**:901-909 (June 20) 1947.

137. Foreign Reports, Pub. Health Rep. **62**:625 (April 25) 1947.

Smallpox virus survived for thirty-five days when exposed to daylight and for eighty-four days when kept in the dark.[138] The virus remained viable for a year in crusts of skin kept in the dark at room temperature. These observations show that smallpox may be contracted from sources remote from patients for long periods.

Mumps.—With rare exception, persons whose blood contains complement-fixing antibodies for mumps virus are resistant to infection by natural exposure.[139] Inapparent infections with mumps are undoubtedly common and probably represent about one third of all cases, since about two thirds of tested persons in large groups have antibody in their blood. The skin test in adults gives an even more sensitive indication of past infection. Persons who exhibit an erythematous dermal reaction to inactivated mumps virus may be regarded as resistant to mumps within an error of 2 to 10 per cent depending on the intensity of the reaction. The skin test itself may evoke a degree of resistance to mumps.

Formalized virus vaccine increased resistance to mumps in about half of a group of vaccinated persons.[140] An improved vaccine against mumps prepared by attenuation during prolonged serial cultivation in embryonated eggs gives promise of greater practical value.[141] Vaccine has been prepared from egg cultures which induces specific immunity in monkeys.[142] Swelling of the parotid gland in inoculated monkeys which were vaccinated was less as compared with that in control animals. An unusual case of primary viral mastitis from mumps was reported.[143]

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138. Downie, A. W., and Dumbell, K. R.: Survival of Variola Virus in Dried Exudate and Crusts from Smallpox Patients, Lancet **1**:550-553 (April 26) 1947.

139. Maris, E. P.; Enders, J. F.; Stokes, J., Jr., and Kane, L. W.: Immunity in Mumps: Correlation of Presence of Complement-Fixing Antibody and Resistance to Mumps in Human Beings, J. Exper. Med. **84**:323-339 (Oct.) 1946. Enders, J. F.; Kane, L. W.; Maris, E. P., and Stokes, J., Jr.: Immunity in Mumps: Correlation of Presence of Dermal Hypersensitivity and Resistance to Mumps, ibid. **84**:341-364 (Oct.) 1946.

140. Stokes, J., Jr.; Enders, J. F.; Maris, E. P., and Kane, L. W.: Immunity in Mumps: VI. Experiments on the Vaccination of Human Beings with Formalized Mumps Virus, J. Exper. Med. **84**:407-428 (Nov.) 1946.

141. Enders, J. F., and others: Alteration of Virulence with Retention of Antigenicity of Mump Virus After Passage in the Embryonated Egg, J. Immunol. **54**:283-291 (Nov.) 1946.

142. Habel, K.: Preparation of Mump Vaccines and Immunization of Monkeys Against Experimental Mumps Infection, Pub. Health Rep. **61**:1655-1664 (Nov. 15) 1946.

143. Lee, C. M.: Primary Virus Mastitis from Mumps, Virginia M. Monthly **73**:327-328 (July) 1946.

A technic is described for the direct isolation of the virus of mumps in chick embryos.[143a]

Herpes Simplex and Herpes Zoster.—Herpes virus may cause herpes simplex, stomatitis, pharyngitis, a varicelliform eruption, encephalomyelitis and keratitis. In 3 cases vulvovaginitis was caused by the virus.[144] A significant serologic difference between some of the strains indicates the existence of various types of herpes virus, as occurs among most infectious agents.

Herpes virus resided in the brain of a rabbit for nine months after it had been inoculated.[145] During this time attacks of encephalitis, presumably of herpetic origin, were precipitated by each of three induced anaphylactic reactions. This circumstance seems to be analogous to the presumed carrier state of herpes simplex virus in man. The virus apparently becomes invasive and pathogenic when provoked by other factors. Klauder[146] reports similar circumstances with herpes zoster. He describes 8 patients in whom the lesions appeared at the site of trauma after one to fourteen days and cites similar observations by others. Although a virus has never been proved to be the cause of herpes zoster, there is much in favor of the view, and to the extent discussed, the analogy to the behavior of herpes simplex as just mentioned is close.

In a patient with herpes zoster meningoencephalitis developed eight days after vaccination with vaccinia virus.[147] Presumably vaccine caused the agent of herpes zoster to invade the central nervous system, but perhaps it was vaccinia virus which invaded it.

Yellow Fever.—A major epidemic of yellow fever extending over 5,000 square miles (12,950 sq. kilometers) occurred in Nigeria in 1946.[148] It was the first known large outbreak of classic urban yellow fever transmitted by Aedes aegypti in fifteen years. The infection is

143a. Leymaster, G. R., and Ward, T. G.: Direct Isolation of Mumps Virus in Chick Embryos, Proc. Soc. Exper. Biol. & Med. **65**:346-348 (June) 1947.

144. Slavin, H. B., and Gavett, E.: Primary Herpetic Vulvovaginitis, Proc. Soc. Exper. Biol. & Med. **63**:343-345 (Nov.) 1946; Antigenic Dissimilarity Between Strains of Herpes Simplex Virus, ibid. **63**:345-347 (Nov.) 1946.

145. Good, R. A.: Recovery of Herpes Simplex Virus from Rabbit Brain Nine Months After Inoculation, Proc. Soc. Exper. Biol. & Med. **64**:360-362 (March) 1947.

146. Klauder, J. V.: Herpes Zoster Appearing After Trauma, J. A. M. A. **134**:245-248 (May 17) 1947.

147. Madonick, M. J.: Meningoencephalitis Complicating Herpes Zoster Ophthalmicus After Treatment by Vaccination, Arch. Neurol. & Psychiat. **56**:434-441 (Oct.) 1946.

148. Fosdick, R. B.: The Rockefeller Foundation: A Review for 1946, New York, 1947, p. 21.

believed to be kept active from year to year in monkeys who have the jungle type of yellow fever and is probably transmitted by Aedes africanus or Aedes simpsoni. The latter may transmit the disease to man, from whom the virus is acquired and spread to others by A. aegypti.

Pretibial Fever, or Fort Bragg Fever.—In 1942 Daniels and Grennan reported a benign infectious disease among soldiers in North Carolina. It was believed to be a hitherto undescribed disease, but dengue or some other known infection was suspected by certain critics. Similar outbreaks occurred in 1943 and 1944. The term pretibial fever was facetiously translated as meaning "hot shins," and this is inaccurate since the eruption also occurs on the arms and elsewhere. Now Tatlock [149] brings forth evidence of a "new" virus as the cause. The agent was recovered from the blood of patients and established in laboratory animals and embryonated eggs. The virus when inoculated into volunteers induced a clinical response typical of the naturally acquired disease.

DISEASES OF PRESUMED VIRAL ORIGIN

Viral Hepatitis.—Alsted [150] describes a form of malignant hepatitis in Denmark, particularly in women over 45 years of age. The mortality rate was 50 per cent. He believes the disease to be etiologically and clinically different from the usual form of infectious hepatitis. The cause is unknown. The mortality rate was 61 per cent in Jersild's patients.[150a]

Other fulminant, fatal attacks of hepatitis of both the infectious and the homologous serum kind were described by Lucké and Mallory.[151] The lesions at necropsy were the same in both kinds. By biopsy made by inserting a hollow needle into the liver in 8 patients with prolonged disease after an attack of viral hepatitis, Volwiler and Elliot [152] found histologic evidence of persisting inflammatory changes. In 2 patients with severe hepatic impairment there were active inflammation and fibrosis. Havens and his co-workers [153] demonstrated acute inflammation

149. Tatlock, H.: Studies on a Virus From a Patient with Fort Bragg Fever (Pretibial Fever), J. Clin. Investigation **26**:287-297 (March) 1947.

150. Alsted, G.: Studies on Malignant Hepatitis, Am. J. M. Sc. **213**:257-267 (March) 1947.

150a. Jersild, M.: Infectious Hepatitis with Subacute Atrophy of the Liver: Epidemic in Women After the Menopause, New England J. Med. **237**:8 (July 3) 1947.

151. Lucké, B., and Mallory, T.: Fulminant Form of Epidemic Hepatitis, Am. J. Path. **22**:867-946 (Sept.) 1946.

152. Volwiler, W., and Elliot, J. A.: Late Manifestation of Epidemic Infectious Hepatitis, paper read before the American Society for Clinical Investigation, May 5, 1947.

153. Havens, W. P.; Kushlan, S. D., and Green, M. R.: Experimentally Induced Infectious Hepatitis: Roentgenographic and Gastroscopic Observations, Arch. Int. Med. **79**:457-464 (April) 1947.

of the wall of the stomach (gastritis) reontgenographically and gastroscopically as one of the features of the acute stage of viral hepatitis. The condition may last into convalescence.

Studies on the prevention of hepatitis with immune globulin show that the immunity afforded against homologous serum jaundice is low as contrasted with that afforded against the infectious type.[154]

Unconvincing report of the transmission of hepatitis to animals was published.[155] Duodenal fluid from patients was said to cause hepatitis in young pigs and white mice. Virus bodies were said to be seen in the duodenal fluid and in the hepatic lesion.

Mononucleosis and Lymphocytosis.—A patient convalescent from infectious mononucleosis was killed in an accident.[156] Necropsy studies revealed the disease to be a generalized one as reported by others previously. There were focal cellular infiltrations in the liver, kidneys, heart, lungs, adrenals, testes and brain. Lesions in the heart and brain are reported for the first time. These systemic involvements account for the variable clinical manifestations of the disease, which may simulate hepatitis, nephritis, myocarditis and viral pneumonia. Evidence of the placental transmission of infectious mononucleosis was observed.[157]

Several more cases of acute infectious lymphocytosis were observed. A small outbreak of 6 cases occurred in England,[158] and 1 involving an adult was observed in this country.[159] The disease occurs chiefly in children and is benign but sometimes prolonged. Swelling of the lymph nodes, an exanthem and lymphocytosis are its characteristics.

Myocarditis.—In Gore's opinion [160] myocarditis occurs more often during acute infectious diseases than recent views indicate, particularly since the term myocarditis often is not used in its restricted sense to indicate actual inflammation. He presents evidence of myocarditis occurring during acute tonsillitis and nasopharyngitis and, as well known, in scarlet fever, diphtheria and meningococcemia. Myocarditis was also

154. Duncan, G. C., and others: An Evaluation of Immune Serum Globulin as a Prophylactic Agent Against Homologous Serum Hepatitis, Am. J. M. Sc. **213**:53-57 (Jan.) 1947.

155. Pendl, O.: Etiology of Contagious Hepatitis, Wien. klin. Wchnschr. **58**:669-672 (Nov. 8) 1946.

156. Allen, F. H., and Kellner, A.: Infectious Mononucleosis: An Autopsy Report, Am. J. Path. **23**:463-478 (May) 1947.

157. Trinção, C.: Infectious Mononucleosis in Puerperium, with Subclinical Infection of the Newborn Infant, Lisboa méd. **23**:146-152 (March) 1946.

158. Steigman, A. J.: Acute Infectious Lymphocytosis in England, Lancet **2**:944 (Dec. 28) 1946.

159. Yaskis, A. S.: Acute Infectious Lymphocytosis in an Adult, J. A. M. A. **132**:638-640 (Nov. 16) 1946.

160. Gore, I.: Myocarditis in Infectious Diseases, Am. Practitioner **1**:292-298 (Feb.) 1947.

found during tuberculosis, relapsing fever, coccidioidomycosis, malaria and a variety of other diseases.

Lyon reports [161] a case of "virus" myocarditis in infectious mononucleosis as recognized by electrocardiographic changes. The first demonstration of interstitial mononuclear cell myocarditis in mononucleosis was made by Allen and Kellner,[156] as stated on a previous page. Smadel and Warren [162] reported on a "new" virus which caused encephalomyocarditis (E.M.C. virus) in a chimpanzee. Curiously, serum from 17 of 44 soldiers who had what was called "three day fever" in the Philippine Islands in 1946 neutralized the virus specifically, which suggested that the same virus caused their undiagnosed malady.

Reiter's Disease.—It is still uncertain if Reiter's disease is an entity caused by a virus or by pleuropneumonia-like organisms or if it is a sequel to bacillary dysentery. In one study [163] agglutinin for a strain of a pleuropneumonia-like organism was found in 4 female patients who had various combinations of colitis, arthritis, conjunctivitis, urethritis, cervicitis and lesions of the skin, 2 of whom had what was suggestive of Reiter's disease at it is reported in man. Agglutinin was not present in patients with urethritis or colitis without other involvement.

Dutch physicians point out,[164] as others have before, that a syndrome resembling Reiter's disease occasionally follows attacks of bacillary dysentery. When this occurs, the disease may last for months. Urethritis, polyarthritis and conjunctivitis may occur in sequence, separately or all at once. According to others,[164a] Reiter's disease is always dysenteric in origin, yet in a study of 900 patients [165b] only 3 had arthritis and in none were the eyes involved. In the present confusion with respect to Reiter's disease it may be better to regard it as a syndrome caused by a number of agents.

Abacterial Pyuria.—This puzzling condition, brought to attention by Wildbolz in 1933, is discussed in six papers.[165] Because bacteria

161. Virus Myocarditis, Foreign Letters, J. A. M. A. **133**:496 (Feb. 15) 1947.

162. Smadel, J. E., and Warren, J.: The Virus of Encephalomyocarditis and Its Apparent Causation of Disease in Man, abstracted, program of the American Society for Clinical Investigation, 1947, p. 31.

163. Wallerstein, R.; Vallee, B., and Turner, L.: Possible Relationship of Pleuropneumonia-Like Organisms to Reiter's Disease, Rheumatoid Arthritis and Ulcerative Colitis, J. Infect Dis. **79**:134-140 (Sept.-Oct.) 1946.

164. Koster, M. S., and Jansen, M. T.: Reiter's Disease, Nederl. tijdschr. v. geneesk. **90**:483-484 (May 18) 1946.

164a. Young, R. H., and McEwen, E. G.: Bacillary Dysentery as the Cause of Reiter's Syndrome (Arthritis with Nonspecific Urethritis and Conjunctivitis), J.A.M.A. **134**:1456-1459 (Aug. 23) 1947.

165. McGrim, E. J.: True Infective Abacterial Pyuria, Wisconsin M. J. **45**:845-847 (Sept.) 1946. Fieldsend, A. B.: Abacterial Pyuria Presenting as

(Footnote continued on next page)

cannot be proved to be related causally, some suspect the condition to be of viral origin. Others, impressed by reports of successful treatment with arsphenamine, suspect a spirochete on that weak evidence alone. The evidence is as unimpressive as that favoring fusospirochetal microorganisms as the cause of stomatitis.

RICKETTSIAL DISEASES

Rickettsialpox.—In June 1946 a newly recognized rickettsial disease was discovered in several boroughs of New York city. It is a specific entity which resembles other rickettsial diseases, and it is characterized by a primary lesion on the skin at the site of infection, fever of short duration, sweats, backache, headache, swelling of lymph nodes and a vesiculopapular rash. The causative agent is Rickettsia akari, which is conveyed from rodents by the rodent mite Allodermanyssus sanguineus. The rickettsias were isolated from naturally infected house mice in the vicinity. References to the few papers on the subject are given in Greenberg's [166] and Heubner's [167] reports. There is reason to believe that the disease exists elsewhere but has been unrecognized.

What may be another newly recognized form of "tick typhus" was reported from Australia.[168] The disease was similar to but much milder than tsutsugamushi disease (scrub typhus). An eschar occurs, and the serum agglutinates Bacillus proteus OX19 and not B. proteus OXK.

The first instance of scrub typhus imported by airplane is reported.[168a]

The epidemiology, clinical data, serologic observations and isolation of Rickettsia burneti in an outbreak of Q fever among stock handlers in Texas in 1946 was described in four papers in the March 22 issue of *The Journal of the American Medical Association.* The outbreak was

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"Urethritis," Brit. M. J. **2**:439-494 (Oct. 5) 1946. Coutts, W. E., and Vargas-Zalazar, R.: Abacterial Pyuria with Special Reference to Infection by Spirochetes. Lancet **2**:982-983 (Dec. 28) 1946. Hamm, F. C.: Amicrobic Pyuria, J. Urol. **57**:226-232 (Feb.) 1947. Baines, G. H.: Abacterial Pyuria from a New Angle. Brit. J. Urol. **19**:6-21 (March) 1947. Goldstein, A. E.: Reiter's Disease Followed by True Infective Abacterial Pyuria, ibid. **19**:32-36 (March) 1947.

165b. Zia, S. H., and Smyly, H. J.: Arthritis in Association with Bacillary Dysentery, Nat. M. J. China **17**:307-312, 1931.

166. Greenberg, M.; Pellitteri, O.; Klein, I. F., and Huebner, R. J.: Rickettsialpox—A Newly Recognized Rickettsial Disease: II. Clinical Observations, J. A. M. A. **133**:901-906 (March 29) 1947.

167. Huebner, R. J.; Jellison, W. L., and Armstrong, C.: Rickettsialpox: A Newly Recognized Rickettsial Disease, Pub. Health Rep. **62**:777-780 (May 30) 1947.

168. Andrew, R.; Bonnin, J. M., and Williams, S.: Tick Typhus in North Queensland, M. J. Australia **2**:253-258 (Aug. 24) 1946.

168a. Dumanis, A. A.: A Fatal Case of Scrub Typhus Introduced into the United States, Ann. Int. Med. **27**:137-142 (July) 1947.

explosive, and the mode of infection was not discovered. Cattle were suspected as the source. Of 136 persons exposed, 55 became sick and 2 died. Most of them had mild disease resembling influenza. Roentgenographic evidence of pulmonary involvement was present in most of the patients studied in the hospital.

Clinical studies show that 9 patients with Rocky Mountain spotted fever treated with paraaminobenzoic acid recovered in shorter time than those untreated.[169] Improvement seemed to begin shortly after the start of therapy. A level of 30 to 60 mg. per hundred cubic centimeters of blood is desired. Methylthionine chloride (methylene blue) was found to be superior to paraaminobenzoic acid in the treatment of experimental tsutsugamushi disease in mice.[170] Methylene blue had been reported to be of value in the treatment of typhus and other diseases by investigators ten or fifteen years ago. In other unpublished experimental studies (Smadel) a combination of streptomycin and paraaminobenzoic acid was more effective in experimental therapy of rickettsial diseases than either agent alone.

Gilliam [171] reports some degree of protection against louse-borne typhus in Cairo after three doses of the Cox type vaccine. One or two doses were not satisfactory. According to Sadusk [4] no deaths from typhus occurred in American soldiers between 1942 and 1945. In those years there were 64 cases of epidemic typhus, 603 cases of murine typhus and 6,685 cases of tsutsugamushi disease. The mildness of most attacks of epidemic typhus was ascribed to the use of antityphus vaccine. The author describes 5 cases of mild typhus in persons who had been supposedly adequately vaccinated. There is no evidence of the value of vaccine for the epidemic type of typhus as a prophylactic agent against murine typhus. Further report [171a] on the treatment of typhus with paraaminobenzoic acid shows the results of therapy to shorten the disease and lower the mortality rate, but when mathematic methods must be used to show "statistical significance," the agent obviously is not as effective as it was hoped. The authors emphasize the importance of beginning treatment early, of keeping the amount in the blood over

169. Flinn, L. B.; Howard, J. W.; Todd, C. W., and Scott, E. G.: Para-Aminobenzoic Acid Treatment of Rocky Mountain Spotted Fever, J. A. M. A. **132**:911-915 (Dec. 14) 1946.

170. McLimans, W. F., and Grant, C. W.: Therapy of Experimental Tsutsugamushi Disease (Scrub Typhus), Science **105**:181-182 (Feb. 14) 1947.

171. Gilliam, A. G.: Efficacy of Cox-Type Vaccine in the Prevention of Naturally Acquired Louse-Borne Typhus Fever, Am. J. Hyg. **44**:401-410 (Nov.) 1946.

171a. Snyder, J. C., and others: Further Observations on the Treatment of Typhus Fever with Para-Aminobenzoic Acid, Ann. Int. Med. **27**:1-27 (July) 1947.

10 mg. per hundred cubic centimeters for epidemic typhus and over 35 mg. for scrub typhus and of keeping the urine alkaline or neutral during treatment. Contraindications to therapy are crystals of para-aminobenzoic acid in the urine, a leukocyte count under 3,000 and a fall of the polymorphonuclear cells to below 25 per cent.

MISCELLANEOUS SUBJECTS

Malaria.—A summary of the advances in the knowledge of malaria gained chiefly during the war years was published by Sapero.[172] Of importance is the information that the life cycle of certain plasmodia is not so simple as it seemed. A developmental cycle apart from the erythrocytic one apparently takes place in endothelial and tissue cells, in which the plasmodia of the vivax type are invulnerable to the well known antimalarial drugs. This fact probably explains the failure of quinine and quinacrine hydrochloride to cure the disease and to prevent relapses. There also have been shown to be variations in strains of Plasmodium vivax malaria to account for the striking clinical and therapeutic differences of the disease in the South Pacific as compared with malaria indigenous in the United States.

Presumed exoerythrocytic forms of malarial parasites in human blood and in tissue culture have been seen and described by several investigators.[172a]

Quinine, quinacrine hydrochloride and chloroquine act principally on plasmodia in the erythrocytic phase and are suppressive whereas pamaquine, "paludrine," (N_1p-chlorophenyl-N_5-isopropyl biguanide) and pentaquine act principally on the forms in the cells and tissue and are curative, especially in P. vivax malaria. Plasmodium falciparum malaria is more easily prevented and cured than other varieties with quinacrine or chloroquine. Great progress was made in the technic of epidemiologic control of malaria with preparations of the insecticide DDT. (4, 4′-dichlorodiphenyltrichloroethane). Repellents are of less value unless they are used under expert direction and thoroughness. Drug prophylaxis with quinacrine hydrochloride successfully prevents clinical attacks of malaria when applied according to prescription. Choloroquine is just as effective and does not discolor the skin; it can be given effectively as a weekly dose. "Paludrine" may prove to be superior. With coordination of efforts at entomologic control and drug therapy, malaria, like tuberculosis, could be eradicated from some areas in a generation.

I have observed a patient in whom chloroquine failed to control relapse of P. vivax malaria acquired in China and caused distressing

172. Sapero, J. J.: The Malaria Problem Today: Influence of Wartime Experience and Research, J. A. M. A. **132**:623-627 (Nov. 16) 1946.

172a. Dubin, I. N.: Bodies Suggesting Exoerythrocytic Forms of Plasmodium Vivax in Tissue Culture, Proc. Soc. Exper. Biol. & Med. **65**:154-156 (June) 1947.

toxic effects. In other studies [173] the synthetic drugs SN 6911 (3-methyl-4-[4-diethylamino-1-methylamino]-7-chloroquinidine), chloroquine and SN 8137 (4-[3-diethylamino-2-hydroxypropylamino]-7-chloroquinoline) were no more effective than quinacrine hydrochloride in controlling relapses of P. vivax malaria of foreign origin. Benign tertian malaria may develop more than a year after suppressive therapy is stopped.[174]

In certain parts of Italy where engineering projects controlling swamps were destroyed during the war malaria is now over fifty times more common than in 1939.[148]

A supplemental issue of the *American Journal of Tropical Medicine* for May deals with malaria in the South Pacific area.

Schistosomiasis.—Faust [175] reviews the literature on the subject of schistosomiasis and describes clinical studies on soldiers who contracted the disease in Leyte in the Philippines. Since the chronic form may appear in some of the victims long afterward, physicians should be aware of its signs and symptoms if they are encountered in men who have served in endemic areas.

Studies from Puerto Rico [176] show that the guppy (Lebistes reticulatus) feeds on egg masses laid by schistosome-bearing snails and on the cercarias shed by the snails. The guppy may be of importance in controlling these sources of Schistosomiasis mansoni.

Trichinosis.—Three epidemics of trichinosis were reported. The largest outbreak in New Fork city in years occurred in March 1945.[177] Eighty-four cases were recognized. Infection was caused by eating uncooked pork sausage. Edema of the eyelids, fever and eosinophilia were the commonest findings. Gastrointestinal symptoms were inconspicuous. The precipitin reaction, because of its earlier appearance, was more useful in diagnosis than the skin test.

An epidemic of trichinosis in mild form occurred in a prison camp.[178] Of 587 men, at least 139 were infected demonstrably, and 100 others were

173. Gordon, H. H.; Dieuaide, F. R.; Marble, A.; Christianson, H. B., and Dahl, L. K.: Treatment of Plasmodium Vivax Malaria of Foreign Origin: A Comparison of Various Drugs, Arch. Int. Med. **79**:365-380 (April) 1947.

174. Scheifley, C. H.: Malaria: A Note on Its Latency and Report of a Case, Proc. Staff Meet., Mayo Clin. **22**:49-52 (Feb. 5) 1947.

175. Faust, E. C.: Schistosomiasis Japonica: Its Clinical Development and Recognition, Ann. Int. Med. **25**:585-600 (Oct.) 1946.

176. Oliver-Gonzalez, J.: Possible Role of the Guppy, Lebistes Reticulatus on the Biological Control of Schistosomiasis Mansoni, Letters to the Editor, Science **105**:605 (Dec. 20) 1946.

177. Shookhoff, H. B.; Birnkrant, W. B., and Greenberg, M.: Outbreak of Trichinosis in New York City with Special Reference to Intradermal and Precipitin Tests, Am. J. Pub. Health **36**:1403-1411 (Dec.) 1946.

178. Hathaway, F. H., and Blaney, L.: Trichinosis: Report of an Epidemic, Ann. Int. Med. **26**:250-262 (Feb.) 1947.

probably infected, as indicated by the presence of eosinophilia. The disease was at first mistaken for nasopharyngitis, sinusitis and malaria, but eosinophilia and swollen lids soon suggested the correct diagnosis. Fever, headache, malaise, muscular pain and swollen lids were the commonest symptoms. Diarrhea occurred in only 14 per cent. There was a similar but smaller outbreak in Sweden.[179] Some victims had muscular discomfort for eight months afterward.

Syverton and his co-workers [180] show that Trichinella spiralis is able to harbor the virus of lymphocytic choriomeningitis and to convey it when fed to animals. It is possible but unproved that this may be one of the natural modes of transmission of the viral disease, akin to Shope's demonstration of the existence of influenza virus in lung worms of swine.

Hookworm Disease.—Hookworm disease as a cause of death was described in 21 children of Guam.[181] Terminal pulmonary infection often obscured the underlying disease. The chief lesions were acute jejunitis, with ulceration and necrosis, and peritonitis. Eosinophilic invasion was a prominent histologic feature.

Leptospirosis.—The first case of Leptospira canicola infection was recorded from England, involving a boy who bathed in the Thames.[182] Diagnosis was made by the development in the serum of an agglutinin for the leptospira. Penicillin apparently was curative. Infection in another patient, most likely contracted from his sick dog, was diagnosed on clinical and serologic evidence.[183]

Toxoplasmosis.—Adams, Horns and Eklund [184] studied a patient aged 14 with toxoplasmosis and investigated other members of the family as well. Positive reactions to the neutralization test were demonstrated with the blood of the patient's mother and with that of 8 of 9 siblings, none of whom were sick or had signs of disease. The results suggest that infection probably occurred subclinically or in unrecognized form in most members of the family and may have been acquired either

179. Wird, K.: Trichinosis Epidemic in Borås District, Acta med. Scandinav. **126**:1-16 (Oct. 15) 1946.

180. Syverton, J. T.; McCory, O. R., and Koomen, J.: The Transmission of the Virus of Lymphocytic Choriomeningitis by Trichinella Spiralis, J. Exper. Med. **85**:759-769 (June) 1947.

181. Zimmerman, H. M.: Fatal Hookworm Disease in Infancy and Childhood on Guam, Am. J. Path. **22**:1081-1101 (Nov.) 1946.

182. Baber, M. D., and Stuart, P. D.: Leptospirosis Canicola: Case Treated with Penicillin, Lancet **2**:594-596 (Oct. 26) 1946.

183. Rosenbaum, H. D.: Canicola Fever: Case Report and Review of Literature, Arch. Int. Med. **78**:531-543 (Nov.) 1946.

184. Adams, F. H.; Horns, R., and Eklund, K.: Toxoplasmosis in a Large Minnesota Family, J. Pediat. **28**:165-171 (Feb.) 1946.

before or after birth. The disease is probably much more common than is generally believed and is often obscured by evidence of hydrocephalus, psychomotor disturbances, encephalitis, pneumonia and an exanthem.

A general review of toxoplasmosis was published.[185]

Steves and Lynch [186] call attention to a generally unrecognized but alarmingly widespread epidemic of ringworm of the scalp. The infection has appeared apparently for the first time in many communities. It is resistant to treatment. A rare case of leptomeningitis caused by the fungus of corn smut is reported.[187]

Wound Infections.—A series of papers in *The Journal of the American Medical Association* of January 25 deal with the problem of infected war wounds. Bacteria isolated from wounds are divided into three groups: A. The toxigenic and/or invasive ones are of greatest importance and can be controlled best by repeated surgical toilet of the wound and its closure. Locally applied chemotherapy is ineffective and deleterious. Penicillin given parenterally is the treatment of choice to supplement surgical treatment. If certain pathogens are highly resistant to penicillin, other agents are necessary. The only prophylactic procedure of value is the use of tetanus toxoid against tetanus. B. The proteolytic group of bacteria either alone or in symbiosis seem to cause septic decomposition of dead tissue and may become pathogenic. C. The group of commensals usually are saprophytic but may act synergistically with others and become invasive. Study of the problem is complicated and time-consuming because of the technic involved in anaerobic cultures and the slowness of growth of many varieties. The bacteria most frequently encountered were beta hemolytic streptococci, staphylococci, enteric streptococci, Clostridium, Proteus, Pseudomonas and coliform bacilli. Certain bacteria which are usually regarded as pathogenic may be present without becoming invasive.

Dienes [188] describes a different and more complex form of reproduction than the ordinarily recognized biniary fission of gram-negative bacteria. Bacilli were seen to swell into large round bodies in which bacteria formed inside, or the swollen forms disintegrated into frag-

185. Callahan, W. P.; Russell, N., and Smith, M. G.: Human Toxoplasmosis, Medicine **25**:343-398 (Dec.) 1946.

186. Steves, R. J., and Lynch, F. W.: Ringworm of the Scalp: Report of Present Epidemic, J.A.M.A. **133**:306-309 (Feb. 1) 1947.

187. Moore, M.; Russell, W. D., and Sachs, E.: Chronic Leptomeningitis and Ependymitis Caused by Ustilago, Probably U. Zeae (Corn Smut): Ustilagomycosis; The Second Reported Instance of Infection, Am. J. Path. **22**:761-778 (July) 1946.

188. Dienes, L.: Reproductive Processes in Proteus Cultures, Proc. Soc. Exper. Biol. & Med. **63**:265-270 (Nov.) 1946.

ments which after a few divisions developed into regular bacteria or a variant form thereof.

Proteus bacilli may form colonies surrounded by a halo composed of filamentous forms which break into short rods and multiply as such. Large bodies attached to filaments may also form at the edges of certain opposing colonies. This suggests the participation in the formation of new forms of bacilli from the two adjacent colonies. The bodies may develop into regular bacilli or may produce the L type of growth. It is unlikely that the meeting of strains and the formation of peculiar forms represent a sexual process of multiplication.

Transformation of bacterial types is known to occur. Such changes had been suspected as accounting for the variability of the colon group of bacilli and have now been demonstrated.[189]. By growth in special media, certain gram-negative bacilli were said to transform themselves into colon bacilli. The phenomenon of variation and transformation plays an important role in the resistance of bacterial strains to antibiotic agents as discussed earlier in this review. It also involves difficulties in the classification of bacteria by causing an instability of types hitherto regarded as fixed.

By electron photomicrography it was shown how the protoplasm of a single bacterial cell is transferred into sperm-shaped bacteriophage particles after the cell is invaded by one or more of them.[190]

Diet.—Schneider [191] points out the variable conditions which must be considered in studies of natural resistance as they pertain to the host and to its potentially invasive bacteria. For statistical studies, contrary to general opinion, the test hosts must not be genetically homozygous and the population of the infecting pathogens must not be uniform but must contain a number of variant forms such as may be expected under natural conditions. In experiments using mice of mixed genetic source and unselected cultures of Salmonella typhi murium, nutritional factors as supplied by selected diets significantly enhanced resistance.

Eisen and his co-workers [191a] were unable to show that adrenal cortical activity has more than a transient effect on the formation of anti-

189. Poe, C. F., and Tregoning, J. J.: Bacterial Variation in Salicin Medium, Proc. Soc. Exper. Biol. & Med. **63**:561-562 (Dec.) 1946.

190. Edwards, O. F., and Wyckoff, R. W. G.: Electron Micrographs of Bacterial Cultures Infected with Bacteriophage, Proc. Soc. Exper. Biol. & Med. **64**:16-19 (Jan.) 1947.

191. Schneider, H. A.: Nutrition of the Host and Natural Resistance to Infection, J. Exper. Med. **64**:305-322 (Oct.) 1946.

191a. Eisen, H. N., and others: Failure of Adrenal Cortical Activity to Influence Circulatory Antibodies and Gamma Globulin, Proc. Soc. Exper. Biol. & Med. **65**:301-306 (June) 1947.

bodies and gamma globulin. Previous studies by White and others had suggested a more important role of the adrenals in this respect.

Pappenheimer [191b] points out that there are only slight quantitative differences in the chemical composition of serum albumin and in some of the strongest poisons known, namely the toxins of diphtheria and botulinus bacilli. There is no clue as to why one protein is toxic and a similar one is not. The toxins of tetanus, diphtheria and botulinus bacilli have been crystallized within the past year.

191b. Pappenheimer, A. M.: Bacterial Toxins, Federation Proc. **6**:479-484 (June) 1947.

Book Reviews

Diagnosis in Sterility. Edited by Earl T. Engle. Conference on Problems in Human Fertility, Sponsored by the National Committee on Maternal Health, January 26-27, 1945, New York. Price, $5. Pp. 248, with 63 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

Dr. Harvey Cushing once remarked that the chief justification for the specialist was his ability to do research; he should explore new fields in medicine, always striving to make the results of his explorations promptly useful to men in general practice. To those interested in the broad aspects of internal medicine this viewpoint is sound.

The management of sterility is not a new specialty. Every internist in the course of his work encounters couples who are baffled by their apparent inability to have children. A group of physicians, including pathologists and biochemists as well as clinicians, have become sufficiently aware of this to form a society under the auspices of the National Committee on Maternal Health. This volume presents the record of the first meeting.

It makes a readable book, describing how the problems of sterility can now be scientifically attacked, the methods currently used, such as semen analysis and testicular or endometrial biopsy and the proper type of history to be taken in studying the infertile couple. It ends with a general summary by Dr. John Rock, of Boston. Dr Rock's concluding sentence emphasizes the continued need for common sense in dealing with a clinical matter in which emotion may often play an essential part. As he says, functional defects in the reproductive apparatus are not recognizable by most of the objective tests, and it is only in function that the reproductive organs can be judged.

Research and Regional Welfare. Papers Presented at a Conference on Research at Chapel Hill, May 9-11, 1945. (University of North Carolina Sesquicentennial Publications.) Edited by Robert E. Coker. Price, $3. Pp. 229. Chapel Hill, N. C.: University of North Carolina Press, 1946.

When the University of North Carolina celebrated its sesquicentennial, it held, among other events, a three day conference on research. The Concise Oxford Dictionary defines the word as meaning an endeavor to discover facts by scientific study of a subject. Evidently the planners of the conference accepted an equally broad definition, and thus their program included a group of addresses by eminent speakers who were interested in the development of knowledge in a variety of different fields.

The addresses are printed in this book. In general, they point to research as the key to the future; they emphasize particularly, however, the importance to the South of research in nutrition and public health, in the humanities and social sciences, in the physical sciences and industry and in the biologic sciences.

The volume makes a valuable collection; certainly it should find a place in every library. Physicians are likely to read with particular care Dr. R. M. Wilder's paper on the importance to public health of research in nutrition, General J. S. Simmon's paper on the foundation for progress in health and public welfare in the South and Mr. D. E. Lilienthal's paper on the moral responsibility of research.

Those who have any special concern with the use of the English language will find the book unusually stimulating. Each contributor is a man of distinction. Even an amateur student of literature will be struck by the differences in literary style adopted by a state governor, a university president, a professor of English, a professor of history, a professor of medicine and a national figure in industry. No

two describe the same idea in the same words, and their construction of sentences, punctuation and vocabulary differ widely. Yet they all demonstrate the basic values of brevity, clarity and unity in the art of writing.

The **Physiological Basis of Medical Practice.** By Charles Herbert Best and Norman Burke Taylor. A Univesity of Toronto text in applied physiology. Fourth edition. Price, $10. Pp. 1,169. Baltimore: Williams and Wilkins Company, 1945.

In this new (fourth) edition the authors have revised and enlarged on previous editions in order to present adequately the rapidly increasing advances in the field of physiology. It continues to be an excellent textbook of physiology from the conventional laboratory viewpoint. It does not, however, give the clinical viewpoint which the title suggests, nor does it afford the desired bridge from laboratory observation to clinical observation on patients or to therapy based on physiologic knowledge.

It is unfortunate that authors of textbooks of physiology do not more frequently have the clinical viewpoint and the knowledge of clinical problems and clinical literature which can come only from close contact with clinical problems and from carrying the responsibility of solving those problems. This is not a criticism, for no one man, even an "admirable Crichton," could possibly cover adequately the entire field of laboratory physiology and its application to the problems of clinical physiology daily met by the physician or surgeon. It might be done by one person covering only a limited section. It might be best to provide a separate course and separate text to serve as a bridge between classroom physiology and its bedside application. Aside from all this, "the physiological basis of medical practice" could possibly be more clearly demonstrated than it is in the text.

Peptic Ulcer: Its Diagnosis and Treatment. By I. W. Held, M.D., and A. Allen Goldbloom, M.D. Price, $6.50. Pp. 382, with 110 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

This is a business-like volume discussing from a variety of viewpoints not only peptic ulcers of the stomach and duodenum, with their varied complications, but also peptic ulcers of the esophagus and of Meckel's diverticulum and gastrojejunal ulcers.

The contents are divided largely on the basis of the relative importance of the individual chapters. For example, the pathogenesis of ulcer is given considerable space, as is roentgenologic diagnosis, while physical findings and other laboratory procedures receive less attention; the pathology of ulcer is passed over quickly, while the treatment of hemorrhage is described in detail. The authors are internists and have prepared their book more for the benefit of fellow internists than for the benefit of surgeons; hence the technic of surgical procedures is given little emphasis. The methods of treatment which are advocated are described carefully and are based on common sense and experience.

The book is readable. It has a well chosen bibliography and a comprehensive index.

Familial Nonreaginic Food-Allergy. By Arthur F. Coca, M.D. Second edition. Price, $3.75. Pp. 191. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

The ARCHIVES (**71**:582 [April] 1943) reviewed the first edition of this book. The author believed that he had been able to assemble a group of cases of food allergy which differed in several respects from cases of atopic allergy. The method of recognition depended on the reaction of the patient's pulse rate to the administration of suspected antigens. The prediction was made that the book would be provoking but that its ideas would have to be confirmed before its concepts could be generally accepted.

The second edition is a revision of the first. With engaging frankness, the author confesses that his earlier work was greeted by his colleagues with uncompromising skepticism. He feels, however, that an interest in the subject is now stirring, and this has led him to the second publication.

His ideas continue to need confirmation.

Unlike most new editions, the present one is $1.25 less expensive than its predecessor in spite of its twenty-five page growth in length.

A Future for Preventive Medicine. By Edward J. Stieglitz. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, $1. Pp. 77. New York: Commonwealth Fund, 1945.

This small volume was printed under the auspices of the Commonwealth Fund. It contains a lecture delivered at the New York Academy of Medicine as part of a series on the general topic of medicine in the future. Evidently it was prepared for public consumption and thus is written in simple, nontechnical language. It makes pleasant reading.

The changes in public health which have taken place in the last forty years are emphasized by simply constructed tables, and the hazards to the health of an aging population are duly stressed. Looking to the future, the author gives chief emphasis to the value of research and education to public health. He believes that good health can be given to no one; it is the task of the individual to earn it, and his ability to do this will depend to an increasing degree on his intelligence, energy and desire as means for preventing disease are further developed.

Every publication of the Commonwealth Fund is attractively printed and well indexed. This monograph is no exception.

Women in Industry: Their Health and Efficiency. By Anna M. Baetjer, Sc.D. Issued under the auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research of the National Research Council. Prepared in the Army Industrial Hygiene Laboratory. Price, $4. Pp. 344. Philadelphia: W. B. Saunders Company, 1946.

This monograph is a critical review of information on the suitability of women for employment. In certain months of 1944 and 1945, 18,000,000 women were employed, more than one third of the total female population 14 years of age or more of the United States. Many of these women performed types of work which heretofore have been considered suitable only for men. This has focused attention on problems which arise not only because of physiologic processes peculiar to women but because of differences between men and women in social background and extra-employment responsibilities. Recent trends suggest that the number of women gainfully employed will continue to be larger than it was before the war, and the data here provided should assist in the formation of policies for the employment of women. It also is expected that the book will stimulate research and the collection of statistics greatly needed in this field.

Of special interest to the reviewer were the following observations: Women fatigue more rapidly than men, probably largely because of household duties and responsibilities which require many hours of work outside those spent in industry. Most authorities recommend a maximum of forty-eight working hours for employed women and restriction of working time to six hours per day in the case of those who have the care of children or sick or aged persons. Rest periods appear to be advantageous, and an adequate luncheon period is essential. Equal pay and equal opportunity for advancement in comparison with those for men are essential in obtaining maximal output. The mortality rate for men of every age is higher than it is for women. Women are ill more frequently and lose more time from work because of sickness. However, their absences are shorter in duration. The reason for the excess absenteeism due to sickness among women as compared with men is not entirely clear. The excess sickness is not limited to diseases related to sexual functions but occurs for diseases common to both sexes. Some persons

have attributed the excess absenteeism because of sickness to poorer nutritional habits on the part of women. Industrial injuries causing disabilities of one day or longer accounted for less than 1 per cent of all disabilities among female employees, and there is no reliable evidence to support the generally accepted view that women are more susceptible than men to occupational diseases.

It is obvious that pregnancy places a definite limit on a woman's ability to do physical work, but there is no reason why a pregnant woman should not continue certain types of work if they are properly controlled and if the industrial physician supervises her placement. Employed women have fewer children than others, but this does not of necessity imply that the low fertility among them results from employment. It more probably indicates merely that women who do not have children enter industry more frequently than do those with children.

The book is fully documented and undoubtedly will prove useful to physicians in and out of industry as well as to managers of personnel departments.

The Diagnostic and Prognostic Meaning of the Demonstration of Tubercle Bacilli in Gastric Lavage in Adults. By Oli Hjaltested. Copenhagen, Denmark: Ejnar Munksgaards Forlag, 1941.

The work demonstrates the unmistakable value of gastric lavage in the diagnosis of pulmonary tuberculosis in adults. An attempt was also made to see if the method had any prognostic implications, but without success. At least more can be determined by repeated roentgenologic study, in which the trends in the character of the lesions can be followed. Patients having gastric washings negative for tubercle bacilli frequently became worse, while as many patients having material which was positive for the organisms improved. There is no doubt that the stage of evolution of the disease had more to do with prognosis than the presence or absence of bacilli.

The records of the controls, including those who gave positive and those who gave negative reactions for tubercle bacilli, were thoroughly studied and documented. The author has confirmed the established fact that tubercle bacilli are not found in persons with no evidence of disease in the lungs even though they may work around infected persons.

The material proper was divided into three groups (exclusive of controls) as follows:

(1) Patients with "hazy" pulmonary fields but without infiltrations.

(2) Patients with pleurisy, who were subdivided into patients with and without visible infiltrations.

(3) Patients with definite parenchymal infiltrations, who were subdivided into patients without visible cavitation, those with doubtful cavitation and those with definite cavitation.

The patients without any visible cavitation (making up most of the group) were divided into fifteen subgroups according to the lung and lobe involved, the degree and character of lesions and the involvement of the hilus.

Exclusive of the controls and the nontuberculous patients, there were 577 "negative" patients, of whom the author found 211 had tubercle bacilli, or 36.5 per cent. The figure is lower than the 48.7 per cent found by Stadnichenko, Cohen and Sweany (published one year earlier, *J. A. M. A.* **114**:634-639 [Feb.] 1940). In their almost identical series of 511 cases there were 249 patients who harbored tubercle bacilli (nearly 25 per cent of those giving positive reactions).

For material so much alike, the difference of 12.2 per cent is considerable. The cause may be due to the delay of twenty-four or more hours in the transfer of the material to the Serum Institute for culture. Sprick and Towey (*Pub. Health Rep.* **61**:648, 1946) obtained 39 per cent poorer results by allowing specimens to stand at room temperature twenty-four hours before neutralizing than by working the specimen up at once. In forty-eight hours their results were 67 per cent worse. Storage of the specimens in ice boxes in the intervening time no doubt prevented much spoilage, but the delay in working up the material seems to have vitiated the authors' otherwise good work.

It is always difficult to say when and under what conditions the last living tubercle bacillus will die in any specimen or when the last living tubercle bacillus has been grown by any given method of culture. Perhaps the best method today will be improved on tomorrow. When fresh material is used on animals, however, the error is never great.

A final word should also be said regarding the possibility of the presence of avirulent saprophytes in gastric washings. They are not common, but they occur sufficiently often to indicate that a test for virulence should be done on all atypical cultures of acid-fast bacilli found in the sediment obtained by gastric lavage.

Barring a few minor imperfections, the work is to be highly commended, not only because it is complete but because it places deserved emphasis on gastric lavage as a means of diagnosis in pulmonary tuberculosis.

Diseases of the Digestive System. Edited by Sidney A. Portis, M.D., F.A.C.P. Second edition. Price, $11. Pp. 932, with 182 illustrations. Philadelphia: Lea & Febiger, 1944.

It is good to see a second edition of this valuable book to which so many able men have contributed. One wishes for time in which to read it from cover to cover because the many chapters are so full of thought-producing ideas. Every young man who aspires to be a gastroenterologist will do well to read and reread this book. It is particularly valuable because the chapters have been written by men much interested in the subject assigned to each. Today no one, no matter how erudite, could hope to cover the whole field well or authoritatively. There has been so great an increase in knowledge that no one can hope to keep up with the literature even of a specialty such as gastroenterology. Because of this, every research worker, teacher and leader must, to a large extent, specialize within his specialty.

It is good to note fine chapters on the anatomy and physiology of the several sections of the digestive tract and also several chapters on the nervous and psychic influences which upset digestion.

The chapter on allergy leaves much to be desired because the author clings to the now well discredited idea that skin tests are of decided value in finding the offending foods and only mentions Rowe's elimination diets. He does not even mention the probably much more helpful diary method. In later editions of the book this serious defect should be remedied. Unfortunately, few of the allergists, whose main concern is the treatment of hay fever and asthma, seem to have made any intelligent effort to grapple with the problems of sensitiveness to foods.

Older gastroenterologists who, in all their years of talking intimately to nervous and psychopathic patients, have never heard one of them speak of the weird ideas of oral receptions and rectal giving that so dominate the writings of Dr. Alexander may experience considerable anorexia and regurgitation when they come to his chapter. They will also wonder how often one really cures a psychopathic patient in whom the disease is hereditary when one listens by the hour to his bizarre ideas. Like the famous author of *The Locomotive God,* he is likely to be still psychotic after he has had his mental catharsis.

But these wonderings of a pessimist and a doubting Thomas must not be allowed to obscure for a moment the delight over this volume and the admiration for the skill with which, in these extremely busy war years, Dr. Portis got so much good work out of so many good men.

Renal Hypertension. By Eduardo Braun-Menendez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Munoz and Alberto C. Taquini. Translated by Lewis Dexter, M.D. Price, $6.75. Pp. 483, with 107 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

Few names, if any, are more outstanding in the modern study of hypertension than those of the group who have worked in the Institute of Professor Houssay in Buenos Aires. In this monograph under the authorship of Braun-Menendez and

his associates, a full and intensively documented account of the development of the subject is given. The thoroughness of the discussion can be inferred from the bibliography of over twelve hundred references. The experimental work on hypertension and the clinical implications are reviewed. There are numerous charts, tables, diagrams and graphs illustrating the text, and the format of the book and the large type are attractive. Dr. Dexter is to be congratulated on his excellent translation and thanked by English-speaking readers for bringing within their scope this admirable monograph.

Peripheral Vascular Diseases. By Edgar V. Allen, Nelson W. Barker and Edgar A. Hines Jr. Price, $10. Pp. 871, with 386 illustrations. Philadelphia: W. B. Saunders Company, 1946.

As a whole, this monograph is good. The authors attempted to cover the field of vascular diseases with completeness, but like all single volume monographs on such an extensive subject, the book fails to be complete. The approach to the problem is, as would be expected, a good version of the approach to the various problems at the Mayo Clinic. For that reason, many differences of opinion which originate elsewhere are not completely considered. The authors have failed to assay adequately the many therapeutic, diagnostic and mechanistic approaches to and opinions of the vascular diseases for the physician who is little acquainted with the problems. In their attempt to make the monograph encyclopedic, they present many ideas without fully evaluating or summarizing the problems for the physicians and students who are unable to do so. A number of methods of diagnosis and treatment presented are useless, but known to be valueless by only the experienced clinicians. As in any book, there are certain errors which have crept in. On page 742, for instance, appears the statement that cold does not depress transmission of nerve impulses, and on page 747 (fig. 327) an elastic bandage is shown held in place by a nondistensible cotton tape, which must obstruct venous return if it supports the bandage. Such errors, however, are obvious and the result of carelessness. As a whole, the monograph is good and should prove to be of value to physicians and students concerned with vascular diseases.

Pneumoperitoneum Treatment. By Andrew L. Banyai, M.D. Price, $6.50. Pp. 376, with 74 illustrations. St. Louis: The C. V. Mosby Company, 1946.

Not many years ago, medical students were taught that patients with peritoneal tuberculosis were often remarkably improved when air was placed within the peritoneal cavity. After a time this form of treatment passed into disuse, and pneumothorax or some form of collapse therapy for pulmonary tuberculosis and other intrathoracic diseases came to the front. Now, perhaps, the pendulum is swinging the other way; at least, here is a book describing the therapeutic value of the former approach.

Its contents are divided into two parts: The first deals with basic principles and the second with therapeutic application.

The first part gives an excellent account of the history of pneumoperitoneum and deals with technic and with the changes in physiology induced by the artificial introduction of air into the abdominal cavity. One gathers that in the hands of an expert the intraperitoneal injection of air is not difficult and that serious complications, such as air embolism or mediastinal emphysema, are rare.

The second part describes the various diseases in which pneumoperitoneum may be used therapeutically. These range from tuberculosis within the abdominal cavity to conditions within the chest; in fact, pulmonary tuberculosis, abscess of the lung, bronchiectasis and even bronchial asthma have on occasion seemed to prove amenable to such treatment.

The concluding chapter is one of bibliography. There are many titles listed, more from foreign than from domestic literature and predominantly old rather than new.

The book is interesting because it is well written and is a sincere piece of work. The author evidently believes in the value of this particular method of treatment for a variety of unrelated disorders and states his views honestly, and thus has assembled a useful textbook, informative as well as helpful for reference.

Die spezielle Pathologie und die Verletzungen der Mundgebilde. By Anton Fonio. Price, 12.80 Swiss francs. Pp. 200, with 12 illustrations. Bern: Verlag Hans Huber, 1945.

This is an interesting book, written by the professor of surgery at the University of Bern (Switzerland). It discusses diseases of the oral cavity, including those of the teeth, tongue, lips, cheeks and tonsils. Little reference is made to work in this territory accomplished on this side of the Atlantic, so that, on the whole, the volume portrays only the European viewpoint toward oral medicine.

The contents are planned logically and deal with many topics on the borderline between dentistry and medicine. One of the book's most engaging features is that no differentiation is made between dentistry and medicine or surgery, the underlying purpose being to discuss the diagnosis and treatment of diseases of the oral cavity whether the latter be by diet, drugs, hygiene or mechanical means. One gets the impression that oral medicine is expanding rapidly abroad and that cooperative effort between dentists, physicians, surgeons and oral hygienists is accomplishing a great deal.

A Primer for Diabetic Patients. By Russell M. Wilder, M.D. Eighth edition. Price, $1.75. Pp. 192, with 8 illustrations. Philadelphia: W. B. Saunders Company, 1946.

Anything of Dr. Wilder's requires no recommendation, and indeed this primer for diabetic patients is known to all as a valuable guide. The most noteworthy addition in this edition is the remarks on the use of mixed insulins. The book should be equally useful for patient and physician.

The American Hospital. By E. H. Lewinsky-Corwin. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, $1.50. Pp. 226. New York: Commonwealth Fund, 1946.

This handsomely printed little monograph keeps up well with the standards of book-making set by the Commonwealth Fund. Sponsored by the Committee on Medicine and Changing Order of the New York Academy of Medicine, the object of this publication is to give a concise, factual summary concerning American hospitals. This is well done in chapters on the development of hospitals and in presentation of data on size, distribution, operating costs, house staff and other factors. There are comprehensive lists of references at the end of each chapter. The book, on the whole, is written from the standpoint of the technical expert and unfortunately deals only in a limited way with some of the most important problems of medicine. The author does not clearly show the fundamental difference of purpose between the university teaching hospital and other hospitals. In his discussion of house staff he does not definitely point out the vital difference between training select men to be future teachers and investigators in medicine and merely preparing physicians in a routine way to qualify for the so-called specialty boards. Too much emphasis is placed on the authority of the specialty boards and other appraising organizations, which after all, with the best intentions, have centered attention on standardization rather than on development of the outstanding few on whom the entire future of medicine depends.

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